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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

June 27, 2007

SUBJECT: Allethrins: Revised HED Chapter of Reregistration Eligibility Decision Document (RED). for Bioallethrin (0040003), Esbiol (004004), Esbiothrin (004007), and Pynamin Forte (004005) and Section 3 Registration Action for Use in Food Handling Establishments: Esbiothrin and Esbiol. DP Barcode: D337992

FROM: Kit Farwell, D.V.M., Toxicologist/Risk Assessor
Timothy Dole, C.I.H., Occupational Residential Exposure Assessor
Toiya Goodlow, Chemist
Reregistration Branch 1
Health Effects Division (7509P)

THROUGH: Michael Metzger, Branch Chief
Reregistration Branch 1
Health Effects Division (7509P)

TO: Molly Clayton, Chemical Review Manager
Reregistration Branch 3
Special Review and Reregistration Division (7508P)
and
Ann Sibold, Chemical Reviewer
Insecticide Branch
Registration Branch (7505P)

This document is the human health risk assessment for the allethrin series of pyrethroid insecticides, Bioallethrin (004003), Esbiol (004004), Esbiothrin (004007, formerly 004003/004004), and Pynamin Forte (004005). This risk assessment evaluates existing uses for the above allethrins as well as a proposed Section 3 registration action for the use of Esbiothrin and Esbiol in food handling establishments (FHE). This assessment has been revised to incorporate risk assessment and risk mitigation changes that have occurred since the end of the public comment period.

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1.0 EXECUTIVE SUMMARY

This human health risk assessment is being conducted as part of EPA's human health risk assessment for the Allethrins Reregistration Eligibility Decision (RED) and a proposed Section 3 registration action for the use of Esbiothrin and Esbiol in food handling establishments (FHE). This document addresses the human health risks associated with allethrins based on label prescribed uses. This document has been revised to include the following risk assessment and risk mitigation changes.

Risk Assessment Changes

1. The POD for chronic dietary and intermediate term incidental oral exposures has been changed from 6.0 mg/kg/day to 8.0 mg/kg/day based upon a benchmark dose analysis.
2. A developmental neurotoxicity (DNT) study is required for the allethrins. However, the Agency is currently evaluating whether a DNT or another comparative toxicity study measuring different endpoints would be best suited for addressing the concern for sensitivity to young animals.

Risk Mitigation Changes (To be included in the Allethrin RED)

1. The residential PCO product labels will be limited to a 0.1 percent spray dilution rate, and language to labeling will be added reducing the volume from 1 gallon per 1000 ft^2 to 0.5 gallon per 1000 ft^2.
2. The maximum spray dilution for indoor fogging applications will be reduced from 3.0 percent (as listed on the Esbiol 300 Insect label #432-870) to 1.5 percent.
3. The consumer surface and space sprays, which currently range from 0.05 percent to 0.5 percent ai in products, will be limited to 0.25 percent ai.
4. The consumer product labels will be changed to require spot treatment only. The broadcast surface applications to rugs and carpets will be eliminated.
5. The use of the 6 ounce outdoor total release fogger will be deleted from the Raid Yard Guard label (4822-394).
6. The pet uses (aerosols sprays and shampoos) will be cancelled. The pet bedding uses will remain as spot treatments.

Allethrins: The allethrin series of pyrethroid insecticides assessed in this document include Bioallethrin (004003), Esbiol (004004), Esbiothrin (004007, formerly 004003/004004), and Pynamin Forte (004005). This risk assessment evaluates existing uses for the above allethrins as well as a proposed Section 3 registration action for the use of Esbiothrin and Esbiol in food handling establishments (FHE).

The allethrins all have the same chemical structure but have several isomers which are "mirror images" of each other. The allethrins differ only in the percentage of isomers present in each pesticide (see Table 2.2b).

Allethrin was the very first pyrethroid to be developed in 1949 and is structurally very similar to cinerin I in naturally occurring pyrethrum. The allethrins cause immediate but temporary paralysis of insects ("knockdown" action), but are not "kill" agents for insects, so they are usually formulated with a synergist and/or with other pyrethroids to prevent recovery by insects. The allethrins are classified as type I pyrethroids because they lack an α-cyano substituent. They degrade rapidly in sunlight.

Uses: Allethrins are used to control flying and crawling insects in a number of commercial, horticultural and residential applications. Commercial applications include space, broadcast and crack and crevice treatment in a variety of commercial, industrial and institutional sites. Horticultural applications include foliar and fogger treatment on non-food plants. Residential uses include pest control in homes and outdoor domestic structures, and on gardens. There are also proposed uses of Esbiothrin and Esbiol in food handling establishments as space or general spray, spot and/or crack and crevice treatment. Allethrins are formulated as liquid concentrates, ready to use aerosol sprays, pet shampoos and dips, mosquito coils and mosquito mats.

Hazard: A number of new toxicity studies have been received since the allethrins were last evaluated by the Hazard Identification Assessment Review Committee in 1997. The toxicity database is most complete for Esbiothrin and Pynamin Forte. The d-trans d- isomer, which is present in the greatest concentration in Esbiol (see Table 2.2b), is reportedly more insecticidally active than the other 3 main isomers.

Similar types of toxicity (neurotoxicity and liver toxicity) occurred at generally similar doses with the different allethrins and data from all four chemicals were used to select endpoints and assess potential sensitivity for FQPA considerations. Clinical signs of neurotoxicity were seen in rat and dog studies, and occurred at lower doses after gavage or capsule dosing than after exposure in the feed. Liver toxicity in subchronic and chronic rat, mouse, and dog studies included microscopic liver changes, elevated liver enzymes, and increased liver weight.

Genetic toxicity studies with Esbiol, Esbiothrin, Bioallethrin, and Pynamin Forte were negative for mutagenicity. Carcinogenicity studies were conducted with Esbiothrin and Pynamin Forte. The only evidence of carcinogenicity was the appearance of rare benign kidney tumors in male rats treated with Esbiothrin. Doses in the mouse carcinogenicity study were considered inadequate and Esbiothrin is classified as having "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential".

Developmental toxicity included rib/rib-vertebral anomalies in a rabbit developmental study with Pynamin Forte. No developmental toxicity was noted in rats treated with Esbiol, Esbiothrin, or Pynamin Forte or in rabbits treated with Esbiol or Esbiothrin. In a reproductive study with Esbiothrin, decreased viability and a marginal increase in delayed developmental milestones occurred. Decreased pup body weights occurred in a reproduction study with Pynamin Forte.

Endpoints: The endpoints for risk assessment were based on neurotoxicity and liver toxicity. Because endpoints for risk assessment were at the same or lower dose at which developmental and reproductive toxicity occurred, there were no concerns for sensitivity of offspring. The allethrins are neurotoxicants and a DNT or comparative neurotoxicity study in adults and offspring is required. A database uncertainty factor of 10x was applied to the points of departure used in dietary and residential assessments to account for the lack of this study.

No systemic toxicity was noted in dermal exposure studies with Esbiol, Esbiothrin, or Pynamin Forte and risk assessments by the dermal route of exposure were not required. Clinical signs of neurotoxicity occurred in an inhalation study with Esbiol.

Drinking water: The registered uses of the allethrins are not expected to adversely impact groundwater or surface water; therefore, a qualitative drinking water assessment was not performed.

Food exposure: Although acute dietary exposure analyses are not ordinarily required for food handling uses, the application of allethrins as a space spray produced relatively high residues, and an acute dietary assessment was therefore conducted. The acute analysis assumed that 100% of food handling establishments and all foods were treated with allethrins. DEEM default processing factors were incorporated. Anticipated residues were determined based on the magnitude of residue study for food handling establishment uses, which analyzed milk, butter, cooked and uncooked meat, flour, rice, bread, lettuce, cooked and uncooked apples, candy and sugar. The highest residue values from each commodity were translated to other foods when appropriate. For foods forms that could not be translated, the highest residue value of 0.93 ppm was used. Dietary risk estimates were determined considering exposures from food only; no exposure to drinking water is expected as a result of allethrins application.

For dietary assessments, HED is concerned if dietary risk exceeds 100% of the Population Adjusted Dose (PAD). For the allethrins, acute dietary risk estimates were below the Agency's level of concern. The highest exposure and risk estimates were for children 1-2 years old. At the 95th percentile, the exposure for children 1-2 years of age was 0.027 mg/kg/day, which utilized 90% of the acute population adjusted dose (aPAD).

A partially refined chronic dietary exposure assessment was also performed. The assessment included average residue values from the FHE magnitude of residue study. It was also assumed that all foods and 20% of all food handling facilities were treated with allethrins based on an estimate by the Biological Effects and Analysis Division (BEAD). Default DEEM processing factors were incorporated. Chronic dietary risk estimates were below the Agency's level of concern. The highest exposure and risk estimates were for children 1-2 years old: exposure was 0.0024 mg/kg/day, which utilized 31% of the chronic population adjusted dose (cPAD).

Residential handlers: An assessment was conducted for handlers who mix, load, and apply allethrins in a residential setting. Only inhalation exposures were assessed for the residential handler scenarios. Dermal exposures were not assessed because no systemic toxicity occurred at the limit dose in dermal toxicity studies. Data from the Pesticide Handlers Exposure Database were used because chemical-specific monitoring data were not available. Residential handler exposures were assessed for aerosol can application to a variety of use sites. This application is protective of risks from trigger sprayer applications because the unit exposure values are lower for trigger sprayer application. All of the handler MOEs exceed the target MOE of 1000 and are not of concern at baseline.

Residential post application: The term "post application" describes individuals who are exposed to pesticides after entering areas previously treated with pesticides. Allethrin post application incidental oral exposures may occur after surface applications of allethrin are made to residential areas such as carpets and vinyl flooring. Inhalation exposures may occur after space spray and outdoor fogger applications. Incidental oral exposures were assessed for toddlers and inhalation exposures were assessed for adults and toddlers. The MOEs were all greater than the target MOE of 1000 except for inhalation exposures from yard and patio total release fogger application where the MOE is 650.

Residential Risk Characterization: The yard and patio fogger scenario is only of concern when the product is in the form of a total release fogger. The yard and patio scenario is not of concern when the product is in the form of a hand held fogger. Although both product forms are on the same label (4822-394) the hand held form is more typically found on retail shelves and likely represents the majority of usage. This is supported by the Residential Exposure Joint Venture (REJV) survey which indicated that most of the Allethrin containing Yard and Patio Fogger products in the house hold inventory were hand held foggers. The hand held fogger contains approximately 454 grams of product which is enough for approximately 9 sprays based upon the nozzle discharge rate of 6 grams per second and a spray duration of 9 seconds By contrast, the total release foggers can only be used once because they discharge their entire contents upon activation. It should also be noted that the NOAEL of 1.3 mg/kg/day observed in the inhalation study may be an artifact of dose spacing because it is five times lower than the LOAEL of 6.5 mg/kg/day. Given that the MOE is 650 with a NOAEL of 1.3 mg/kg/day, only a slightly higher NOAEL of 2.0 mg/kg/day would yield an MOE of 1000. Considering this, HED has minimal concern with an MOE of 650 for this scenario.

Aggregate exposure: Aggregate assessments were conducted for incidental oral exposure scenarios because the same study is used for the dietary and incidental oral exposure endpoints based on liver toxicity in dog studies. Inhalation exposure was not aggregated because the endpoint for inhalation exposure was based on a different effect (neurotoxicity). Aggregate risk was calculated for combined food and residential exposure for children 1-2 years old because this age group had the highest dietary exposure and could be expected to receive incidental oral exposure. No endpoints were identified for dermal exposure and the allethrins are not expected to adversely impact ground water, so exposure by these routes was not aggregated. The short term aggregate MOEs are not of concern for any of the scenarios because they exceed the LOC of 1000 An intermediate term aggregate MOE of 750 was estimated for one scenario (PCO Broadcast – Carpet). There is minimal concern for this estimated risk, however, since the intermediate term (continuous exposure over a one to six month period) exposures of toddlers to day zero carpet surface residues is highly unlikely due to dissipation. The MOE of 750 is expected to be protective for this exposure scenario.

Occupational handlers: Although the term "handler" applies to individuals who mix, load, and apply the pesticide product, most allethrin products are packaged in aerosol cans, so most of the allethrin uses involve only application. There are a few products packaged as ready to use liquids or liquid concentrates, which are applied with mechanical sprayers, compressed air sprayers or foggers. These products are used in commercial/industrial/ institutional areas, non-food greenhouses and non-food animal premises.

Only inhalation exposures were assessed. Most of the inhalation MOEs are above the target MOE of 100 without respirators and therefore the inhalation risks are not of concern. The high pressure handwand scenario is of concern without respirators and requires a dust mask to achieve the target MOE. The space spray fogger scenario is also of concern and requires a PF50 full face respirator with appropriate cartridges to achieve the target MOE.

Occupational post application: Occupational post application inhalation exposure was assessed for a metered release scenario. The MOE is 850, which exceeds the target MOE of 100 and is not of concern.

2.0 INGREDIENT PROFILE

2.1 Summary of Registered/Proposed Uses

Target Pests and Use Sites:

Insecticides containing allethrins are used to control flying and crawling insects at a variety of occupational and residential use sites as listed below:

Domestic (household): Crawling and flying insect killers for use indoors as space, general surface, spot and crack & crevice applications; on house plants and residential greenhouses. Crawling and flying insect killers for use outdoors as localized space and contact spray, perimeter treatments (sidewalks, decks, patios, outside surfaces of buildings, etc.), and application to ornamental plants.

Commercial/Industrial/Institutional: Crawling and flying insect killers for use indoors as space, general surface, spot and crack & crevice applications. Also for use on indoor plants. Crawling and flying insect killers for use outdoors as localized space and contact sprays and perimeter treatments (sidewalks. entranceways, outside surfaces of buildings, etc.). Also for use on ornamental plants in landscaped areas.

Greenhouses: Use in commercial greenhouses to control various plant pests on ornamentals as a space and/or contact spray.

Food Handling Establishments: There are proposed uses of Esbiothrin and Esbiol in food handling establishments as space or general spray, spot and/or crack and crevice treatment. A food handling establishment is any place other than a residential kitchen in which food is held, processed, prepared, and/or served.

Formulations

Allethrins are formulated as emulsifiable concentrates, liquid concentrates, pressurized liquids, ready to use liquid sprays, pet shampoos and dips, mosquito coils and mosquito mats. The registered products are formulated and used as listed in Table 2.1a.

Formulation	Number of Labels[A]	Use Categories: Domestic Household	Commercial Industrial Institutional	Greenhouse	Animal Treatment[B]
Pressurized Liquid	136	YES	YES	YES	YES
RTU Liquids	31	YES	YES	YES	YES
Emulsifiable Concentrates	3	NO	YES	YES	YES
Liquid Concentrates	6	NO	YES	YES	YES
Shampoos and Dips	22	NO	NO	NO	YES
Mosquito Coils and Mats[C]	15	YES	NO	NO	NO

A. As listed in the Use Closure Memo.
B. Primarily includes cats, dogs and horses. Excludes animals used for food.
C. Listed as impregnated materials in OPPIN.

Smart Meeting Information

A summary of information about application of allethrins obtained from Smart meetings with registrants is included in Table 2.1b.

Table 2.1b. Allethrin Smart Meeting Information

Use	Indoor/ Outdoor	Percent ai	Comments
Crawling Insect Killer Aerosols (Surface Spray)	Both	0.05 to 0.25	Spray until wet (20 to 50 ml/m^2). Droplet size is 50 to 80 micron.
Wasp and Hornet Aerosols	Outdoor	0.05 to 0.1 (water or solvent based)	Spray nest for to 2 – 3 seconds. Discharge rate is 20 grams per second in a jet stream with a range of 15 to 20 feet.
Yard and Patio Foggers (i.e. hand held foggers)	Outdoor	0.1 to 0.15 (water based)	Spray for 2 to 3 sec. at bushes, grass etc. Typical discharge rate is 5-6 gram product per sec. Application rate is 1 to 3 seconds per square meter. Droplet size is 50 to 100 micron.
Flying Insect Killer Aerosols (Space Spray)	Both	0.1 to 0.25 (usually water based)	Spray room for 3-5 sec. Keep room closed for 15 minutes and ventilate (i.e. open windows) prior to re-entry. Discharge rate 1 gram per second. Droplet size is 10 to 25 micron. Not very effective outdoors. Very common overseas. Not common in the U.S.
Total Release Aerosols (i.e. stationary foggers)	Indoor	1.2 to 3.0 (usually water based)	6 ounce can treats 5000 to 6000 ft^3 room. Droplet size is 40 to 50 micron. Vacate room for several hours. Ventilate for 30 minutes.
Mosquito and Fly Repellent Mats	Outdoor	Mosquito 7% Fly 24%	Mats weigh 0.93 grams and last 10 hours. Protect an average patio (15 x 15 ft). Aerosol size is very small (<2 microns).
Mosquito Repellent Coils	Outdoor	0.25 to 0.3 %	Coils weigh 12 grams and burn for 6 to 7 hours.
Pet Spray Aerosols *	Indoor	0.2% water based	Apply directly to animal until hair is moist. Can also be used to treat bedding rugs and carpets. Largely replaced by spot-ons and pills (Frontline, Advantage, Program)
Pet shampoos*	Indoor	0.12%	For use on dogs. Largely replaced by spot-ons and pills.

*** Note - the pet spray and shampoo uses will be cancelled.**

Proposed Uses

A summary of use directions for the proposed uses of Esbiol and Esbiothrin in food-handling establishments are shown in Table 2.1c.

Table 2.1c. Summary of Use Directions for Esbiol and Esbiothrin in Food Handling Establishments.

Application Type	Formulation	Application Rate	Max. No. Application per Season	Max. Seasonal Application Rate	Use Directions and Limitations
Esbiol					
General spray	VBC Esbiol® 90 Insecticide	1.43 % final dilution spray, 1.0 fluid oz. per 1000 ft^3	Not Specified	Not Specified	Note 1
Space Spray					Note 2
Spot Treatment		0.32% final dilution spray, 0.45 fluid oz. per 1000 ft^2			Note 3, 4
Crack and Crevice Treatment		1.43 % final dilution spray, 1.0 fluid oz. per 1000 ft^3			Note 5
Esbiothrin					
General spray	VBC Esbiothrin® 90 Insecticide	1.70 % final dilution spray, 1.0 fluid oz. per 1000 ft^3	Not Specified	Not Specified	Note 1
Space Spray					Note 2
Spot Treatment		0.39% final dilution spray, 0.55 fluid oz. per 1000 ft^2			Note 6,4
Crack and Crevice Treatment		1.70 % final dilution spray, 1.0 fluid oz. per 1000 ft^3			Note 5

Notes

1. Do not apply directly to food/feed. Do not apply as a space spray while food processing is underway. Cover or remove all food and food processing surfaces. Wash all food processing surfaces before reuse. After spraying, wash all surfaces where food will be handled and rinse with potable water rinse prior to use. Except in federally-inspected meat and poultry plants, food/feed processing operations do not have to be stopped.

2. Cover or remove exposed food/feed and cover food handling surfaces. Close rooms and shut ventilating equipment. Apply at application rate of 1.0 oz/1000 ft^3, filling the room with mist. Vacate treated area and ventilate before reoccupying. Keep area closed for at least 1 hour. Repeat treatment if reinfestation occurs. Do not apply while food processing is underway. **In animal quarters** (unoccupied cattle and horse barns, poultry and swine houses, kennels): Cover exposed water, drinking fountains and animal feed before application. Direct spray towards upper portions of the enclosure filling the room with mist. Vacate area and ventilate before reoccupying.

3. Mix 0.45 oz. of concentrate with sufficient oil to equal 1 gallon of diluted spray.

4. Apply as a coarse droplet spray using 1 gallon to 1000 ft^2. Spray walls, floors and other surfaces of bins, storage and handling areas. Treat unloading, handling and processing areas. Also treat inside conveying, processing and handling equipment. Spray around the base of heavy machinery and equipment. Spray insects directly when possible.

5. Treat wall voids, insect tunnels, boxed beams and other hollow elements of construction. Inject voids for 5-10 seconds followed by sufficient air to move particles throughout the void.

6. Mix 0.55 oz. of concentrate with sufficient oil to equal 1 gallon of diluted spray.

2.2 Structure and Nomenclature

The allethrin series of pyrethroid insecticides assessed in this risk assessment include Bioallethrin (0040003), Esbiol (004004), Esbiothrin (004007, formerly 004003/004004), and Pynamin Forte (004005).

The different allethrin pyrethroids differ only in the percentage of stereoisomers present. There are three asymmetric carbons and thus eight potential isomers, although 4 isomers are present in the greatest concentration for these products. The allethrins are structurally very similar to cinerin I in naturally occurring pyrethrum.

Allethrin (004001, no longer registered) was the very first pyrethroid to be developed in 1949. The allethrins cause immediate but temporary paralysis of insects ("knockdown" action), but are not "kill" agents for insects, so they are usually formulated with a synergist and/or with other pyrethroids to prevent recovery by insects. The allethrins are classified as type I pyrethroids because they lack an α-cyano substituent. They degrade rapidly in sunlight.

Table 2.2a. Test Compound Nomenclature

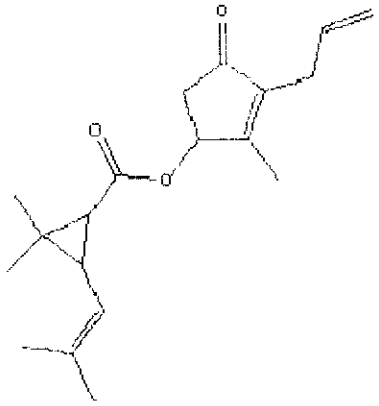
Chemical Structure for the Allethrins	
Empirical Formula	$C_{19}H_{26}O_3$
Molecular Weight	302.4
Chemical Class	type I pyrethroid
Known Impurities of Concern	None

Table 2.2b. Percentage of Isomers for Each Technical Product in the Allethrin Family

Isomer	**Esbiol** (S-Bioallethrin)	**Esbiothrin**	**Bio-allethrin**	**Pynamin Forte** (d-allethrin)
PC Code	004004	004007 [a]	004003	004005
CAS #	28434-00-6	584-79-2	584-79-2	584-79-2
d-trans chrysanthemic acid of **d**-allethrolone [b]	> 90%	72%	≥ 46%	36%
d-trans chrysanthemic acid of **l**-allethrolone	5%	21%	≥ 46%	36%
d-cis chrysanthemic acid of **d**-allethrolone	- - - [c]	- - -	- - -	9%
d-cis chrysanthemic acid of **l**-allethrolone	- - -	- - -	- - -	9%

a PC code for Esbiothrin formerly 004003/004004
b The d-trans d- isomer is reportedly the most insecticidally active; isomer used in plant metabolism study.
c - - - indicates < 2%
Adapted from 1/23/97 William O. Smith memo (D222638).

2.3 Physical and Chemical Properties

Table 2.3. Physical and Chemical Properties

Parameter	Esbiol [a] S-Bioallethrin	Esbiothrin [b]	Bioallethrin [c]	Pynamin Forte [d] d-allethrin
Physical state	viscous liquid	viscous liquid	viscous liquid [a]	liquid
Boiling point	165-170° C	165° C	165° C	281.5° C
pH	4.9	4.5	4.3	4.08
Density	1.010	1.010	1.012	1.009
Water solubility	4.6 mg/L	4.6 mg/L	4.6 mg/L	5.0 mg/L
Vapor pressure mm Hg	3.3×10^{-4}	3.3×10^{-4}	3.3×10^{-4}	1.24×10^{-6}
Dissociation constant	N/A	N/A	N/A	N/A
Octanol/water partition	$K_{OW} = 48000$	$\log P_{ow} > 5$	$\log P_{ow} > 5$	$P_{OW} = 8.94 \times 10^{4}$
UV/visible absorption	not reported	not reported	not reported	not reported

a 2/2/06 Product Chemistry Review, D326386
b 2/27/97 Product Chemistry Review, D226959
c 2/27/97 Product Chemistry Review, D226950
d 12/27/05 Product Chemistry Review, D324618

3.0 HAZARD CHARACTERIZATION/ASSESSMENT

3.1 Hazard and Dose-Response Characterization

Esbiothrin, Esbiol, and Bioallethrin were evaluated together by the Hazard Identification Assessment Review Committee (HIARC) in 1997. Although bridging of toxicity data between the chemicals had previously been done, the HIARC decided not to allow bridging between those three allethrins because of the limited database, especially for developmental and reproductive toxicity studies. Since that time, a number of new studies have been submitted and reviewed which provide a sufficient database for bridging.

New studies with Esbiol include developmental toxicity in rats and rabbits, acute and subchronic neurotoxicity studies, subchronic dermal toxicity in rats, and a subchronic inhalation toxicity study. New studies with Pynamin Forte include a 2- generation reproductive toxicity study in rats, a 21-day dermal toxicity in rabbits, an Ames study, and an inhalation study. There is also a new micronucleus study with Bioallethrin. The inhalation study with Pynamin Forte was recently submitted and classified unacceptable although this study had a higher NOAEL than that from the only other allethrin inhalation study (Esbiol).

The new and old studies with **Esbiothrin** evaluated for this assessment include developmental studies in rats and rabbits, a 2-generation reproduction study in rats, chronic toxicity studies in dogs and rats, carcinogenicity studies in rats and mice, subchronic studies in mice and dogs, a 21-day dermal study in rabbits, and a battery of mutagenicity studies.

The new and old studies with **Pynamin Forte** include developmental rat and rabbit studies, a 2-generation reproduction study in rats, chronic toxicity studies in dogs and rats, carcinogenicity studies in rats and mice, a subchronic dermal toxicity study in rabbits, an inhalation study in rats, and a subchronic feeding study in mice.

The new and old studies with **Esbiol** include developmental studies in rats and rabbits, acute and subchronic neurotoxicity studies in rats, subchronic feeding studies in rats and dogs, subchronic dermal and inhalation studies, and mutagenicity studies.

Bioallethrin studies include a developmental rat study, subchronic studies with rats and dogs, metabolism studies, and mutagenicity studies.

The registrants report that the d-trans d- isomer is more insecticidally active than the other 3 main isomers (d-trans l-, d-cis d-, and d-cis l-). No side-by-side comparisons of the 4 main isomers are available; however, if the d-trans d- isomer is more insecticidally active, then this isomer could cause neurotoxicity at a lower dose than the other isomers. This is not always evident from the toxicity studies which used different doses for the different chemicals and were conducted by different labs in different years.

Clinical signs of neurotoxicity, such as muscle tremors, hunched posture, salivation, were seen in the rat studies which used gavage dosing. Muscle tremors and other signs of neurotoxicity were

noted in dog subchronic and chronic studies and occurred at a lower dose in a capsule study than in feeding studies.

Liver toxicity in subchronic and chronic rat, mouse, and dog studies included increased liver weight, microscopic liver changes, and elevated liver enzymes. Microscopic changes in the thyroid were noted in a subchronic rat study with Esbiol.

Genetic toxicity studies with Esbiol, Esbiothrin, Bioallethrin, and Pynamin Forte were negative for mutagenicity. Carcinogenicity studies were conducted with Esbiothrin and Pynamin Forte. The only evidence of carcinogenicity was rare benign kidney tumors in male rats treated with Esbiothrin. Doses in the mouse carcinogenicity study were considered inadequate and the cancer classification for Esbiothrin is "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential".

Developmental toxicity included rib/rib-vertebral anomalies in a rabbit developmental study with Pynamin Forte. No developmental toxicity was noted in rats treated with Bioallethrin, Esbiol, Esbiothrin, or Pynamin Forte or in rabbits treated with Esbiol or Esbiothrin.

In a reproductive study with Esbiothrin, decreased viability and a marginal increase in delayed developmental milestones occurred. Decreased pup body weights occurred in a reproduction study with Pynamin Forte.

No systemic toxicity was noted in dermal exposure studies with Esbiol, Esbiothrin, or Pynamin Forte. Clinical signs of neurotoxicity occurred in an inhalation study with Esbiol.

3.2 Absorption, Distribution, Metabolism, Excretion (ADME)

Two metabolism studies with Bioallethrin were available. There were no major differences between sexes, between low and high dose groups, nor between single-dose groups and repeated-dose groups. The majority of radioactivity was eliminated within 3 days. Urinary elimination ranged from approximately 25 – 50% and fecal elimination ranged from 50 – 70%. There was no bioaccumulation of residue in tissues. Metabolism was mainly by oxidation of double bonds and isobutenyl methyl groups, by ester cleavage, and by conjugation. Principal metabolites included esters and conjugates of allethrolone and dihydroxy allethrolone, epoxy allethrin, and allethrolone.

3.3 FQPA Considerations

3.3.1 Toxicity Database

There are developmental toxicity studies in rats with Bioallethrin, Esbiothrin, Esbiol, Pynamin Forte; developmental rabbit studies with Esbiothrin, Esbiol, Pynamin Forte; 2-generation reproduction studies with Esbiothrin and Pynamin Forte; and acute and subchronic neurotoxicity

studies with Esbiol. Comparative neurotoxicity studies in adults and offspring are not available for any of the allethrins.

Pyrethroids are neurotoxicants which act by prolonging the opening of the sodium channel in nervous tissue, resulting in a hyperexcitable state. The allethrins are classified as type I pyrethroids because they lack an α-cyano substituent, in contrast to the type II pyrethroids which have an α-cyano substituent. Neurotoxicity of type I pyrethroids is characterized as tremor, prostration, enhanced startle response, and aggressive behavior (Casarett and Doull's Toxicology, 6th edition). Similar signs were observed in the guideline studies in which clinical signs of neurotoxicity were noted.

3.3.2 Developmental and Reproductive Toxicity Studies

Developmental Toxicity with Esbiothrin (rats): In a developmental toxicity study (MRID 41632201), 24 pregnant Crl:CD®BR rats per group were administered Esbiothrin (95.2% a.i.) by gavage at doses of 0, 5, 25, or 125 mg/kg/day on gestation days (GD) 6-15, inclusive. On GD 20, all dams were sacrificed, subjected to gross necropsy, and all fetuses examined externally.

No clinical signs of toxicity or mortalities were observed in the 0, 5, or 25 mg/kg/day groups. One rat died at 125 mg/kg/day (HDT, day 10 of gestation). A significantly ($p \leq 0.01$) increased incidence of tremors (21/25), body jerks (20/25), and hypersensitivity to sound (20/25) were observed in high-dose dams. These observations generally occurred for approximately 4 hours after intubation on days 10 through 15 of gestation and did not persist overnight. Excessive salivation was observed in 0/25, 1/25, 2/25, and 1/25 animals in the 0, 5, 25, and 125 mg/kg/day groups, respectively, and may have been related to treatment. No treatment-related effects were observed on maternal body weight, food consumption, or gross necropsy.

The maternal toxicity LOAEL is 125 mg/kg/day based on clinical signs of toxicity and the maternal toxicity NOAEL is 25 mg/kg/day.

Pregnancy incidences; the average number of corpora lutea, implantations, resorptions and fetuses per litter; the number of dams with viable fetuses; and the litter averages for fetal sex ratios, body weights and percent resorbed conceptuses were comparable with the control group for all treated groups. No treatment-related gross external, soft tissue, or skeletal malformations/variations were observed in fetuses from any dose group.

The developmental toxicity NOAEL is >125 mg/kg/day and the developmental toxicity LOAEL was not identified.

This developmental toxicity study in the rat is classified acceptable (guideline) and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700) in the rat.

Developmental Toxicity with Esbiol (rats): In a developmental toxicity study (MRID 44666301), Esbiol (96.9%) was administered to 22 female CD (SD) rats/dose by gavage at dose levels of 0, 5, 20, or 80 mg/kg bw/day on days 6 through 15 of gestation, inclusive. On GD 20, all surviving dams were sacrificed and examined grossly.

A total of four high-dose dams died prior to scheduled termination. One animal was found dead on GD 7; three others were killed moribund on GDs 7, 9, and 14, respectively. Among high-dose animals that survived to termination, 100% showed tremors and piloerection between GDs 11-15. Clinical signs were absent by about 2 hours post-dosing. All control, low-, and mid-dose animals survived to scheduled termination with no treatment-related clinical signs of toxicity. No treatment-related effects on absolute body weight were observed in any group during the study.

The maternal toxicity LOAEL for Esbiol in Sprague-Dawley rats is 80 mg/kg/day based on mortality and clinical signs of toxicity. The maternal toxicity NOAEL is 20 mg/kg/day.

No treatment-related differences were noted between the treated and control groups for numbers of corpora lutea and implantations, placental and gravid uterine weights, live fetuses per dam, resorptions, fetal sex ratios, and pre- or post-implantation losses. Fetal body weights were similar between the treated and control groups. Developmental toxicity was not identified; there were no treatment-related external, visceral, or skeletal malformations/variations observed in any group.

The developmental toxicity LOAEL for Esbiol in Sprague-Dawley rats is not identified and the developmental toxicity NOAEL is ≥80 mg/kg/day. This developmental toxicity study in the rat is classified Acceptable/Guideline and satisfies the guideline requirements for a developmental toxicity study in rats.

Developmental Toxicity with Pynamin Forte (rats): In a developmental toxicity study (MRID 41225803), Pynamin Forte (93.4) was administered to 25 pregnant Crl:CD(SD)BR rats per dose by gavage from gestation days 6 - 15. Doses were 0, 10, 30, or 100 mg/kg/day.

Maternal toxicity at 100 mg/kg/day included clinical signs (excessive salivation, tremors, body jerks, chromodacryorrhea), and decreased body weight gain. The maternal NOAEL was 30 mg/kg/day. The maternal LOAEL was 100 mg/kg/day based on clinical signs and decreased body weight gain.

No developmental toxicity occurred in this study. Treatment had no effect on pregnancy incidences, number of corpora lutea, implantations, implantation efficiencies, litter sizes, live and dead fetuses, early and late resorptions, fetal body weights, fetal sex ratios, or fetal viability. No teratogenic effects were noted. The developmental NOAEL was 100 mg/kg/day, the highest dose tested. The developmental LOAEL was not determined.

In a rangefinding study, the maternal LOAEL was 50 mg/kg/day, the lowest dose tested, based on clinical signs (salivation) and the developmental NOAEL was 300 mg/kg/day, the highest dose tested.

This developmental toxicity study in rats is classified acceptable/guideline and satisfies guideline requirements for a developmental toxicity study in rats.

Developmental Toxicity with Bioallethrin (rats): In a developmental toxicity study (MRID 00078624), at least 28 pregnant Sprague-Dawley rats per group were administered Bioallethrin (92.5%) by gavage at doses of 0, 50, 125, or 195 mg/kg/day on gestation days (GD) 6-15, inclusive.

No clinical signs of toxicity were observed in animals from the 0, 50, or 125 mg/kg/day groups. An increase in the incidence of maternal mortality occurred in the high-dose group: 0/28, 0/33, 1/33, and 6/34 ($p \leq 0.05$) dams in the 0, 50, 125, and 195 mg/kg/day groups, respectively.

The maternal toxicity LOAEL is 195 mg/kg/day based on increased mortality and the maternal toxicity NOAEL is 125 mg/kg/day.

There were no differences between treated groups and controls for pregnancy rate, numbers of corpora lutea, implantations, live or dead fetuses, or resorptions per dam, and fetal body weights. No treatment-related external or visceral malformations/variations were observed in any fetuses. Rudimentary ribs were increased in all treated groups, however, this was not considered a treatment-related effect. The developmental toxicity NOAEL is 195 mg/kg/day.

There were several major deficiencies in the conduct of this study: dosing solutions were not analyzed for concentration, homogeneity, or stability; food consumption was not measured; gross necropsies were not performed on the dams; individual maternal and fetal data were not included; and number of corpora lutea were not calculated on the summary table. This study is classified Acceptable (nonguideline) and does not satisfy the guideline requirements for a developmental toxicity study in rats.

Developmental Toxicity with Esbiothrin (rabbits): In a developmental toxicity study (MRID 41632202), 20 pregnant New Zealand white rabbits per group were administered Esbiothrin (95.2%) by gavage at doses of 0, 30, 100, and 300 mg/kg/day on gestation days (GD) 6-18, inclusive. Cesarean section was performed on all surviving does on GD 29 followed by teratological examination of all fetuses.

No treatment-related mortalities or clinical signs of toxicity were observed in does in the 0, 30, or 100 mg/kg/day groups. In the 300 mg/kg/day dose group, four does died during the treatment period (3 on GD 9 and 1 on GD 10). A significantly ($p \leq 0.01$) increased incidence of clinical signs of toxicity at the high-dose included tremors (7/20), decreased motor activity (7/20), ataxia (6/20), and impaired righting reflex (4/20). These signs generally occurred about 4 hours postdosing on GD 7-12 and did not persist more than one day.

There were no statistically significant differences attributed to treatment in body weights, body weight gains, or food consumption values between the 30 or 100 mg/kg/day groups and the controls. In the high-dose group, all of the does that died had reduced body weight prior to death. If these animals are excluded from the group means, there were no significant differences in body weights or body weight gains between the high dose group and the controls at any time period. No gross lesions attributable to the test substance were observed in any of the does, including those that died.

The maternal toxicity LOAEL is 300 mg/kg/day based on mortality and clinical signs of toxicity (tremors, decreased motor activity, ataxia, and impaired righting reflex) and the maternal toxicity NOAEL is 100 mg/kg/day.

There were no statistically significant differences between the treated and control groups in pregnancy indices, averages for corpora lutea, implantations, live litter sizes, resorptions, fetal sex ratios, fetal body weights, percent resorbed conceptuses, or the numbers of does with any resorptions or with viable fetuses. There were no fetal gross, external, soft tissue, or skeletal malformations/variations that were considered to be related to treatment.

The NOAEL for developmental toxicity is 300 mg/kg/day (HDT) and the LOAEL was not identified. This developmental toxicity study in the rabbit is classified acceptable (guideline) and satisfies the guideline requirement for a developmental toxicity study in rabbits.

Developmental Toxicity with Esbiol (rabbits): In a developmental toxicity study (MRID 44657801), Esbiol (96.9) was administered to 16 female New Zealand white rabbits/dose by gavage at dose levels of 0, 5, 50, or 200 mg/kg bw/day from gestation days (GD) 6 through 19, inclusive. On GD 29, all surviving does were sacrificed and examined grossly.

No treatment-related deaths occurred in any animal and gross necropsy was unremarkable. One low-dose doe aborted on GD 21 and was sacrificed. Clinical signs of toxicity were limited to tremors in one high-dose animal on GD 19 approximately 30 minutes after dosing. No treatment-related effects on absolute body weight were observed in any group during the study. The high-dose animals had transient decreases in body weight gain after the initiation of dosing. Food consumption by the high-dose group was 86% of the control group level for GD 6-12. A compensatory increase in food consumption occurred in the high-dose group during the post-dosing interval.

The maternal toxicity LOAEL is 200 mg/kg/day based on decreased body weight gain and tremors. The maternal toxicity NOAEL is 50 mg/kg/day.

Treatment had no effect on numbers of corpora lutea, implantations, gravid uterine weights, live fetuses, resorptions, fetal sex ratios, pre- or post-implantation losses, fetal body weights, or external or visceral malformations/variations. The high-dose group had an increased number of litters with incomplete metacarpal(tarsal)/phalangeal ossification (6 litters vs 2 in controls) and an increased number of litters with unossified epiphyses (7 litters vs 4 in controls). There was also an increased number of fetuses with 13 ribs (77 vs 56 in controls) and an increased number of fetuses with 20 thoracolumbar vertebrae (46 vs 36 in controls); litter data for these effects were not available.

The developmental toxicity LOAEL for Esbiol in New Zealand white rabbits is 200 mg/kg/day based on decreased ossification. The developmental toxicity NOAEL is 50 mg/kg/day. This developmental toxicity study in the rabbit is classified Acceptable/Guideline and satisfies guideline requirements for a developmental toxicity study in rabbits.

Developmental Toxicity with Pynamin Forte (rabbits): In a developmental toxicity study (MRID 41225806), Pynamin Forte (93.4) was administered to 20 pregnant NZW rabbits per dose by gavage from gestation days 7 - 19. Doses were 0, 30, 100, or 350 mg/kg/day.

The death of one doe in the high-dose group on day 10 of gestation was attributed to treatment. Body weight gains in the high-dose group were significantly less than controls from gestation days 7 - 10 (-30 g vs +20 g in controls), but were comparable to controls for the entire dosing period (+110 g vs +130 g in controls). Two does in the high-dose group had gastric inflammation or ulceration. The maternal NOAEL is 100 mg/kg/day. The maternal LOAEL is 350 mg/kg/day based on mortality and decreased body weight gain.

Treatment had no effect upon the number of corpora lutea, implantations, resorptions and live fetuses; implantation efficiencies; percentages of live male fetuses; fetal body weights or litter sizes. Rib/rib-vertebral malformations were increased in the high-dose group.

The developmental NOAEL is 100 mg/kg/day. The developmental LOAEL is 350 mg/kg/day based upon increased rib/rib-vertebral malformations. This developmental toxicity study in rabbits is classified acceptable/guideline and satisfies guideline requirements for a developmental toxicity study in rabbits.

Reproduction Study with Esbiothrin: Esbiothrin was tested in a 2-generation reproduction study in rats at 0, 70, 200, 600 or 1800 ppm (0, 5.8, 16.8, 50.4 or 150.0 mg/kg/day for males and 0, 7.4, 22.5, 67.1 or 207.0 mg/kg/day for females).

No treatment-related effects were observed on mortality or clinical signs of toxicity in F_0 or F_1 male or female parents. No treatment-related effects were observed on body weights in treated F_0 males or females. Body weights at 1800-ppm were slightly decreased throughout treatment in F_1 males (92-95% of the control values, $p<0.05$) and on premating days 1, 15, 50, and 99, gestation day 21, and lactation days 1 and 4 in F_1 females (92-93% of control values). There were no treatment-related effects on gross or microscopic findings.

The parental NOAEL is 600 ppm (50.4 mg/kg/day for males and 67.1 mg/kg/day for females) and the LOAEL is 1800 ppm based on decreases in body weights in male and female F_1 parents (150.0 mg/kg/day for males and 207.0 mg/kg/day for females).

There were no treatment-related effects on reproductive performance of either generation. The day 21 viability index for high-dose F_1 pups was significantly decreased. No statistically significant decreases in viability indices were observed for F_2 pups.

F_1 and F_2 pups in the 1800-ppm group showed evidence of delayed development (eye opening, auricular duct opening, and air righting). Body weights of F_1 pups in the 1800-ppm group were significantly less than control values throughout lactation (range: 76% at day 7 to 94% at day 1). F_2 pups in the 1800-ppm group weighed 91 to 93% of control weights throughout lactation. Body weight gain in F_1 pups was reduced by 42% at 1800 ppm during the first 7 days of lactation.

The LOAEL for developmental effects is 1800 ppm (150.0 mg/kg/day for males and 207.0 mg/kg/day for females) based on decreased viability, decreased body weight gain, and delayed developmental milestones of the pups. The corresponding NOAEL is 600 ppm (50.4 mg/kg/day for males and 67.1 mg/kg/day for females).

This two-generation reproduction study in rats is classified acceptable (guideline) and satisfies guideline requirements for a two-generation reproduction study in rats.

Reproduction Study with Pynamin Forte: In a 2-generation reproduction study (MRID 41246801) Pynamin Forte (d-allethrin, 91.9% a.i.) was administered to 30 Crl:COBS® CD®(SD)BR rats/sex/dose in the diet at 0, 200, 2,000, or 6,000 ppm (equivalent to doses of 0, 12.8, 130.0, or 386.7 mg/kg/day for P_1 males; 0, 13.3, 137.0, or 430.5 mg/kg/day for F_1 males; 0, 14.7, 144.6, or 440.1 mg/kg/day for P_1 females; 0, 14.6, 152.4, or 476.9 mg/kg/day for F_1 females).

There was no effect upon reproductive indices. At the 2,000 ppm dose level, treatment-related reductions in body weights and body weight gains were noted in the F_1 females and reductions in body weight gains were noted in the P_1 and F_1 males. For both generations, absolute and relative liver weights were increased and treatment-related hepatocellular hypertrophy was noted (P_1 males only and in both sexes of the F_1 generation).

Parental toxicity at 6,000 ppm for both generations and sexes included reductions in body weights, body weight gains, and feed consumption values; increases in absolute and relative (to body weight) liver weights; and histopathology of the liver described as hepatocellular hypertrophy.

The parental NOAEL = 200 ppm (12.8 mg/kg/day in males and 14.7 mg/kg/day in females) and the parental LOAEL = 2000 ppm (130 mg/kg/day in males and 145 mg/kg/day in females) based on reductions in body weights, body weight gains, increases in absolute and relative liver weights, and hepatocellular hypertrophy.

At 6,000 ppm, treatment-related decreases in mean pup body weights were noted in both the F_1 and F_2 generations. For the F_1 generation litters dosed at the high-dose, the severity of the reductions in body weight increased over time as the pups began to supplement their nutrient intake (milk) with the treated diet ($\downarrow$9% on day 4, $p \leq 0.05$ and $\downarrow$21% on day 21, $p \leq 0.01$). For the high-dose F_2 litters, mean pup body weights were also decreased throughout lactation ($\downarrow$3-18%), however, the differences from the controls were not statistically significant.

The offspring NOAEL is 200 ppm (14.7 mg/kg/day) and the LOAEL for offspring toxicity is 2,000 ppm (145 mg/kg/day) based on reductions in pup body weights of the F_2 generation.

The reproductive study in the rat is classified Acceptable/Guideline and satisfies the guideline requirement for a 2-generation reproductive study (OPPTS 870.3800, §83-4) in rats.

3.3.3 Additional Information from Literature Sources

No relevant information from the open literature was found in a PubMed search.

3.3.4 Pre-and/or Postnatal Toxicity

Developmental: There was no evidence of prenatal susceptibility in developmental rat studies with Bioallethrin, Esbiol, Esbiothrin, or Pynamin Forte; or in a developmental rabbit study with Esbiothrin because no treatment-related developmental toxicity occurred in these studies. There was no evidence of prenatal susceptibility in the developmental rabbit study with Pynamin Forte because rib and vertebral malformations occurred at the same dose as maternal mortality. There was no evidence of prenatal susceptibility in the developmental rabbit study with Esbiol because decreased ossification occurred at the same dose as did maternal neurotoxicity.

Reproductive: There was evidence of postnatal qualitative susceptibility in the 2-generation reproduction study with Esbiothrin: decreased pup viability and delayed developmental milestones occurred at a dose that only caused decreased parental body weight.

There was no evidence of postnatal susceptibility in the 2-generation reproduction study with Pynamin Forte. Decreased pup body weights occurred at the same dose which caused decreases in parental body weight and liver effects.

Degree of Concern Analysis for Pre- and/or Postnatal Susceptibility: There was evidence of susceptibility in the Esbiothrin 2-generation reproduction study. However, there are no residual uncertainties because the NOAELs for dietary exposure (30 and 8 mg/kg/day), incidental oral exposure (20 and 8 mg/kg/day), and inhalation exposure (1.3 mg/kg/day) are all lower than the offspring NOAEL from the reproductive study (50 mg/kg/day).

3.3.5 Recommendation for a DNT or Comparative Neurotoxicity Study

As described above, the allethrins are neurotoxicants which act by prolonging the opening of the sodium channel in nervous tissue, resulting in a hyperexcitable state. Neurotoxicity was observed in a number of dog and rat studies, tremors being the most common sign. Neurotoxicity in the Esbiol acute neurotoxicity study also included hunched posture, abnormal gait, and decreased grip strength. A developmental neurotoxicity (DNT) study is required for the allethrins. However, the Agency is currently evaluating whether a DNT or comparative toxicity study in adults and offspring would be best suited for addressing the concern for sensitivity to young animals.

3.4 Hazard Identification and Toxicity Endpoint Selection

3.4.1 Acute Reference Dose - Females age 13-49

Study Selected: Not applicable

MRID Number: None

Dose and Endpoint for Establishing aRfD: None

Comments about Study/Endpoint/Uncertainty Factor: Rib/rib-vertebral malformations were noted in the Pynamin Forte rabbit developmental study and decreased ossification occurred in the Esbiol rabbit developmental study. These endpoints were not selected because the NOAELs (100 mg/kg/day and 50 mg/kg/day, respectively) were significantly higher than the NOAEL based on neurotoxicity selected for the general population acute reference dose (aRfD). Therefore, the acute dietary assessment based on neurotoxic effects will be protective of developmental effects as well.

3.4.2 Acute Reference Dose - General Population

Study Selected: Acute neurotoxicity in rats (Esbiol)

MRID Number: 44517801

Dose and Endpoint for Establishing aRfD:
NOAEL = 30 mg/kg/day
LOAEL = 90 mg/kg/day based on FOB findings (tremors, hunched posture, abnormal gait, decreased grip strength)

Uncertainty Factor(s): 1000x (10x for interspecies extrapolation, 10x for intraspecies variability, and 10x for lack of a comparative neurotoxicity study)

Comments: The FOB changes are characteristic of the allethrins.

$$\textbf{Acute RfD} = \frac{30 \text{ mg/kg/day}}{1000} = 0.03 \text{ mg/kg/day}$$

Executive Summary: In an acute oral neurotoxicity study (MRID 44517801), Esbiol (S-Bioallethrin; 96.9% w/w a.i., Batch/lot # 6N 0248B) in 1% (w/v) methylcellulose in purified water was administered in a single dose by gavage (10 mL/kg) to fasted Sprague-Dawley CD rats (10/sex/dose) at doses of 0, 5, 30, or 90 mg/kg. All animals were observed for up to 14 days post-dosing. Functional observational battery (FOB) and motor activity were evaluated pretreatment and on Days 1 (at the time of peak effect, approximately 30-60 minutes post-dosing), and days 7 and 14. At termination, 5 rats/sex/group were perfused *in situ* for neurohistological examination. Positive pathology control data were not provided.

At 90 mg/kg, the following transient FOB effects were noted in females on Day 1: increased incidence of slight to moderately hunched posture, slight to moderate body twitches, and severe tremor during homecage observations; slight to moderately abnormal gait, slight to severe tremor, and slight head or body twitches during open-field observations; and increased ($p<=0.01$) body temperature (incr 0.9°C), and decreased hindlimb (decr 22%, $p<=0.05$) and forelimb (decr 12%, NS) grip strength.

No compound-related effects on mortality, clinical signs, body weight, body weight gain, food consumption, motor activity, or gross and histopathology were observed at any dose. No adverse treatment-related FOB effects were noted at Days 7 and 14.

The NOAEL is 30 mg/kg. The LOAEL is 90 mg/kg based on FOB effects (hunched posture, head and/or body twitches, tremor, abnormal gait, increased body temperature, and decreased hindlimb and forelimb grip strength) which occurred on day 1 in females.

Although positive control data demonstrated the ability to detect major neurotoxic endpoints and changes in motor activity, pathology positive control data were not submitted. However, neuropathology has not been noted with other pyrethroids. This study is classified acceptable/non-guideline and satisfies the guideline requirements (OPPTS 870.6200a; OECD 424) for an acute neurotoxicity screening battery in rats.

3.4.3 Chronic Reference Dose (cRfD)

Study Selected: 6-Month dog feeding study (Bioallethrin)

MRID Number: 00151447

Dose and Endpoint for Establishing cRfD:
$BMDL_{10}$ = 8.0 mg/kg/day based on microscopic liver changes (hepatocellular degeneration) for males and females occurring at the mid and high doses.

Uncertainty Factor(s): 1000x (10x for interspecies extrapolation, 10x for intraspecies variability, and 10x for lack of a comparative neurotoxicity study)

Comments about Study/Endpoint/Uncertainty Factor: Liver toxicity occurs in other studies with the allethrins. A $BMDL_{10}$ was used rather than the NOAEL from this study because of the 6x difference between the NOAEL (6 mg/kg/day) and the LOAEL (36 mg/kg/day). A 10% response for the BMDL was selected because of the mild nature of the lesions, characterized as "acute swelling of hepatocytes", which did not progress in severity at the high dose. The lesions were accompanied by increased relative liver weight and moderate increases in alkaline phosphatase in males. The selected $BMDL_{10}$ value was 267 ppm (D339909). This dietary concentration was converted to a mg/kg/day dose by using the dose in males, which was lower than that in females: 267 ppm/200 ppm x 6.1 mg/kg/day = 8 mg/kg/day.

$$\textbf{Chronic RfD} = \frac{8 \text{ mg/kg/day}}{1000} = 0.008 \text{ mg/kg/day}$$

Executive Summary: In an oral toxicity study (MRID 00151447), Bioallethrin (92.5% a.i.) was administered to 6 beagle dogs/sex/dose in the diet at levels of 0, 200, 1000, or 5000 ppm for 6 months. These concentrations resulted in approximate dose levels of 0, 6.1, 36.3, or 162 mg/kg/day for males and 0, 7.2, 36.4, or 172 mg/kg/day for females.

Clinical observations included slight irregular heart rhythms and general body trembling in high-dose males and females and excessive salivation in high-dose males only. The onset of body tremors ranged from weeks 1 to 4 and were last observed between weeks 1 and 27. Decreases in mean body weight gain were observed in mid-dose males and in high-dose males and females, and food consumption was consistently decreased in high-dose males and females. No treatment-related effects on ophthalmology, hematology, urinalysis, or gross pathology were observed.

Increases in mean alkaline phosphatase enzyme activity was observed in mid-dose males (+196%) and high-dose males (+493%) and high-dose females (+382%) compared to controls; this increase is considered toxicologically significant at the high dose. SGPT enzyme activity was increased in high-dose animals males (+367%) and females (+452%) compared to control values. GGTP enzyme activity was increased in high-dose animals but there was considerable variation in control animals and this was not considered toxicologically significant. Increased relative liver weights were observed in mid- and high-dose animals of both sexes. A dose-related hepatocellular degeneration of the liver was observed in mid- and high-dose males and females.

The NOAEL for this study is 200 ppm (6.1 mg/kg/day for males; 7.2 mg/kg/day for females) and the LOAEL is 1000 ppm (36.3 mg/kg/day for males; 36.4 mg/kg/day for females), based on hepatocellular degeneration in both sexes at 1000 ppm and above. Toxicity at the high dose (5000 ppm) also included slight irregular heart rhythms and general body trembling (both sexes), salivation (males), decreases in body weight gain and food consumption (both sexes), and increases in liver enzymes.

This toxicity study is classified acceptable (nonguideline) for a chronic feeding study and acceptable (guideline) for a subchronic feeding study in the dog. It is a well conducted study and was conducted during the time when six month dog studies were considered acceptable as chronic studies.

3.4.4 Incidental Oral Exposure (Short-Term)

Study Selected: 30-day dog feeding study (Esbiothrin)

MRID Number: 43293401

Dose and Endpoint:
NOAEL = 20 mg/kg/day
LOAEL = 63 mg/kg/day based on liver toxicity

Uncertainty Factor(s): 1000x (10x for interspecies extrapolation, 10x for intraspecies variability, 10x for lack of a comparative neurotoxicity study)

Comments about Study/Endpoint/Uncertainty Factor: The duration of exposure was appropriate for this endpoint. Although this was a rangefinding study, it was considered an acceptable study for endpoint selection.

Executive Summary: In a 4-week rangefinding study in dogs (MRID 43293401), Esbiothrin (94.7 to 98.8 %) was administered to two Beagle dogs/sex in the feed at concentrations of 0, 50, 200, 800, 3200 or 6400 ppm (males: 0, 1.3, 4.5, 19.5, 63.2 or 153.2 mg/kg/day; females: 0, 1.5, 5.9, 22.1, 74.8 or 174.0 mg/kg/day.

One male in the high-dose group had clinical signs which began on day 8 and became more pronounced until day 29, when the dog was found dead. Clinical signs usually began 3 hours after eating, lasted about 6 hours and included marked tremors, restlessness and uncoordinated movements. Several days before death, the signs intensified to loss of balance, lateral recumbency, stereotypes of the mouth, clonic convulsions and epileptic seizures. No clinical signs were observed in any other dogs. Body weights in treated animals were generally comparable to controls, although there was a larger overall body weight loss in 6400 ppm males (-1.5 kg) compared to controls (-0.1 kg).

Liver enzymes were elevated in 3200 and 6400 ppm males and females although there was a lot of variability because there were only two dogs/sex/group. Alkaline phosphatase was elevated in 3200 ppm males (184% of controls), in one 3200 ppm female (458%), in 6400 ppm males (312%), and in 6400 females (354%). ALT was elevated in one 3200 ppm male (1317%) and in the 6400 ppm males (312%). Absolute liver weights were elevated in 3200 ppm males (123%) and females (146%), and in the surviving 6400 ppm male (135%) and the 6400 ppm females (200%). Relative liver weights were increased in 3200 ppm males (146%) and females (163%), and in the surviving 6400 ppm male (156%) and the 6400 ppm females (203%). Brown pigments in the hepatocytes and bile canaliculi was seen microscopically in the high-dose dogs, but no toxicologically significant lesions were observed.

The NOAEL is 800 ppm (19.5 mg/kg/day in males and 22.1 mg/kg/day in females). The LOAEL is 3200 ppm (63.2 mg/kg/day in males and 74.8 mg/kg/day in females), based on elevated liver enzymes and increased liver weight. This 4-week rangefinding study in dogs is classified acceptable/non-guideline. It was used for dose selection for the chronic study in dogs.

3.4.5 Incidental Oral Exposure (Intermediate-Term)

Study Selected: 6-Month dog feeding study (Bioallethrin)

MRID Number: 00151447

Dose and Endpoint: $BMDL_{10}$ = 8.0 mg/kg/day based on microscopic liver changes (hepatocellular degeneration) for males and females occurring at the mid and high doses.

Uncertainty Factor(s): 1000x (10x for interspecies extrapolation, 10x for intraspecies variability, and 10x for lack of a comparative neurotoxicity study)

Comments about Study/Endpoint/Uncertainty Factor: Liver toxicity occurs in other studies with the allethrins. A $BMDL_{10}$ was used rather than the NOAEL from this study because of the 6x difference between the NOAEL (6 mg/kg/day) and the LOAEL (36 mg/kg/day). A 10% response for the BMDL was selected because of the mild nature of the lesions, characterized as "acute swelling of hepatocytes", which did not progress in severity at the high dose. The lesions were accompanied by increased relative liver weight and moderate increases in alkaline phosphatase in males. The selected $BMDL_{10}$ value was 267 ppm. This dietary concentration was converted to a mg/kg/day dose by using the dose in males, which was lower than that in females: 267 ppm/200 ppm x 6.1 mg/kg/day = 8 mg/kg/day.

Executive Summary: See chronic dietary section, above, for the executive summary.

3.4.6 Dermal Absorption

There is not an acceptable dermal absorption study with any of the allethrins.
See Comments section for Dermal Exposure section, below.

3.4.7 Dermal Exposure (Short-, Intermediate- and Long-Term)

Study Selected: N/A

MRID Number: N/A

Dose and Endpoint for Establishing cRfD: N/A

Uncertainty Factor(s): N/A

Comments about Study/Endpoint/Uncertainty Factor: Dermal risk assessments are not required because no systemic toxicity occurred in a dermal rat study at 1000 mg/kg/day with Esbiol; or at 1000 mg/kg/day in rabbits with Esbiothrin; or at 300 mg/kg/day (highest dose tested) in rabbits with Pynamin Forte. In addition, there was negligible dermal absorption with the closely related pyrethrin isomers (0.22%). There were no developmental concerns from the Pynamin Forte or Esbiol rabbit developmental studies: rib malformations or decreased ossification occurred at a maternally lethal dose or at a dose causing maternal neurotoxicity.

3.4.8 Inhalation Exposure (Short-, Intermediate- and Long-Term)

Study Selected: 28-Day inhalation study in rats (Esbiol)

MRID Number: MRID 44517802

Dose and Endpoint:
NOAEL = 1.3 mg/kg/day
LOAEL = 6.5 mg/kg/day based on clinical signs in females (limb tremors, hunched posture, vocalization during handling)

Uncertainty Factor(s): 100x for occupational exposure (10x for interspecies extrapolation and 10x for intraspecies variability). 1000x for residential exposure (included 10x database uncertainty factor for lack of a comparative neurotoxicity study.

Comments about Study/Endpoint/Uncertainty Factor: The route of exposure is appropriate for this exposure scenario. An acute inhalation assessment using an endpoint from the acute neurotoxicity study was not performed because the NOAEL from that study (30 mg/kg/day) was much greater than the NOAEL from the inhalation study (1.3 mg/kg/day). An inhalation study with Pynamin Forte is currently classified unacceptable/guideline.

Executive Summary: In a 28-day inhalation toxicity study (MRID 44517802), Esbiol (S-Bioallethrin; 96.9% w/w a.i.; Lot/batch # 6N 0248B) was administered via snout-only inhalation to CD Sprague-Dawley rats (5/sex/concentration) for 6 hours/day, 5 days/week for 4 weeks at analytical concentrations of 0, 0.0051, 0.025, or 0.073 mg/L. Doses were equivalent to 0, 1.3, 6.5, or 19.0 mg/kg/day.

There were no effects of treatment on survival, body weights, body weight gains, food consumption, clinical chemistry, organ weights, gross pathology, or histopathology.

Clinical signs of toxicity in mid- and high-dose females included intermittent tremors in the limbs, hunched posture, and vocalization when handled. Additionally at 0.073 mg/L in these animals, walking on tiptoes and aggressive behavior were observed. Intermittent tremors in the limbs were also noted in the high-dose males.

Additional clinical observations indicated a compromised ability of the rats to maintain a clean, groomed appearance and included increased incidences over controls of: wet and/or matted fur in high-dose males and mid- and high-dose females; brown staining on head in mid- and high-dose females; hair loss on body in the high-dose males; and brown staining around snout in the all male and female treatment groups. At necropsy, badly groomed fur on the dorsum was observed in 3/5 females in the high-dose group.
The LOAEL is 0.025 mg/L (6.5 mg/kg/day) based on increased incidences of clinical signs of toxicity (intermittent tremors in the limbs, hunched posture, vocalization during handling, ungroomed appearance) in females. The NOAEL is 0.0051 mg/L (1.3 mg/kg/day). The submitted study is classified as acceptable/non-guideline (only 5 animals per group) and satisfies the requirements for which it was intended as a 28-day inhalation toxicity study in the rat.

3.4.9 Level of Concern for Margin of Exposure

The target Margins of Exposure (MOEs) for residential and occupational exposure and risk assessment are as follows:

Table 3.4.9 Summary of Levels of Concern for Risk Assessment.

Route of Exposure	Duration of Exposure		
	Short-Term (1-30 Days)	Intermediate-Term (1-6 Months)	Long-Term (>6 Months)
Occupational Exposure			
Dermal (all populations)	N/A	N/A	N/A
Inhalation (all populations)	100	100	100
Residential Exposure			
Incidental Oral	1000	1000	1000
Dermal (all populations)	N/A	N/A	N/A
Inhalation (all populations)	1000	1000	1000

Incidental oral and inhalation MOEs for residential exposure include a 10x database uncertainty factor for lack of a comparative neurotoxicity study.
A dermal risk assessment was not required because there was no systemic toxicity in dermal toxicity studies at 1000 mg/kg/day and because of negligible dermal absorption with pyrethrin (0.22%).

3.4.10 Recommendation for Aggregate Exposure Risk Assessments

An aggregate exposure considers exposure from three major routes: oral, dermal, and inhalation. No endpoints were identified for dermal exposure, so dermal exposure need not be assessed in an aggregate assessment of the allethrins. Because the allethrins are not expected to adversely impact ground water, drinking water will not be included in an aggregate assessment.

A short-term aggregate exposure assessment can be conducted for post application exposure which will include dietary exposure and incidental oral exposure using the endpoint for short-term incidental oral exposure. The NOAEL is 20 mg/kg/day based on liver toxicity in the 30-day dog study with Esbiothrin. Inhalation exposure will not be included because inhalation exposure has a different endpoint (neurotoxicity), however, liver toxicity is the most sensitive endpoint. An intermediate-term aggregate exposure assessment can be conducted for post application exposure which will include dietary exposure and incidental oral exposure. The endpoint uses a $BMDL_{10}$ of 8 mg/kg/day based on liver toxicity in a 6-month dog study with Bioallethrin. As mentioned above, inhalation exposure will not be included because inhalation exposure has a different endpoint (neurotoxicity).

3.4.11 Classification of Carcinogenic Potential

Genetic toxicity studies with Esbiol, Esbiothrin, Bioallethrin, and Pynamin Forte were negative for mutagenicity. Carcinogenicity studies were conducted with Esbiothrin and Pynamin Forte. The only evidence of carcinogenicity was rare benign kidney tumors in male rats treated with Esbiothrin. Doses in the mouse carcinogenicity study were considered inadequate and the cancer classification for Esbiothrin is "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential".

3.4.12 Summary of Toxicological Doses and Endpoints

Table 3.4.a Toxicological Doses and Endpoints for Dietary and Residential Exposure

Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern	Study and Toxicological Effects
Acute Dietary (General Population, including infants and children)	NOAEL = 30 mg/kg	UF_A = 10x UF_H = 10x FQPA SF= 10x [UF_{DB}]	aRfD = 0.03 mg/kg aPAD = 0.03 mg/kg	Acute neurotoxicity in rats (Esbiol). LOAEL = 90 mg/kg based on functional observational battery (tremors, hunched posture, abnormal gait, decr. grip strength)
Chronic Dietary (All Populations)	$BMDL_{10}$ = 8 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 10x [UF_{DB}]	cRfD = 0.008 mg/kg/day cPAD = 0.008 mg/kg/day	6-month dog (Bioallethrin). $BMDL_{10}$ based on based on microscopic liver changes (hepatocellular degeneration)
Incidental Oral Short-Term (1-30 days)	NOAEL = 20 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 10x [UF_{DB}]	Residential LOC for MOE = [1000]	30-day dog (Esbiothrin). LOAEL = 63 mg/kg/day based on elevated liver enzymes and increased liver weight
Incidental Oral Intermediate-Term (1-6 months)	$BMDL_{10}$ = 8 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 10x [UF_{DB}]	Residential LOC for MOE = 1000	6-month dog (Bioallethrin). $BMDL_{10}$ based on based on microscopic liver changes (hepatocellular degeneration)
Dermal (all durations)	N/A	N/A	N/A	No systemic toxicity at 1000 mg/kg/day with Esbiothrin or Esbiol and negligible dermal absorption with pyrethrins (0.22%)
Inhalation (all durations)	NOAEL = 1.3 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 10x [UF_{DB}]	Residential LOC for MOE = 1000	28-day inhalation study in rats with Esbiol. LOAEL = 6.5 mg/kg/day based on clinical signs in females (limb tremors, hunched posture, vocalization during handling)
Cancer (all routes)	Classification: Esbiothrin: suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential.			

The FQPA Safety Factor (FQPA SF) is a database uncertainty factor (UF_{DB}) to account for the lack of comparative neurotoxicity data with the allethrins.

Point of Departure (POD) = A data point or an estimated point derived from dose-response data which is used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (intraspecies). UF_H = potential variation in sensitivity among members of the human population (interspecies). UF_{DB} = to account for the absence of key data FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Table 3.4b Toxicological Doses and Endpoints for Occupational Exposure				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/ FQPA Safety Factors**	**RfD, PAD, Level of Concern**	**Study and Toxicological Effects**
Dermal (all durations)	N/A	N/A	N/A	No systemic toxicity at 1000 mg/kg/day with Esbiothrin or Esbiol and negligible dermal absorption with pyrethrins (0.22%)
Inhalation (all durations)	NOAEL = 1.3 mg/kg/day	UF_A = 10x UF_H = 10x	Occupational LOC for MOE = 100	28-day inhalation study in rats with Esbiol. LOAEL = 6.5 mg/kg/day based on clinical signs in females (limb tremors, hunched posture, vocalization during handling)
Cancer (all routes)	Classification: Esbiothrin: suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential.			

Point of Departure (POD) = A data point or an estimated point derived from dose-response data which is used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (intraspecies). UF_H = potential variation in sensitivity among members of the human population (interspecies). MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

3.5 Endocrine disruption

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there were scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, the allethrins may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 PUBLIC HEALTH AND PESTICIDE EPIDEMIOLOGY DATA

An incident report is being prepared.

5.0 DIETARY EXPOSURE/RISK CHARACTERIZATION

5.1 Pesticide Metabolism and Drinking Water Profile

The nature of the residue in plants is adequately understood for the purposes of the food handling use petition. Metabolism in three different scenarios was studied: applications were made to field grown crops, Petri dishes to investigate photolysis *in vitro*, and stored foods. Allethrin and several photoproducts were identified in the field metabolism portion of the study. Allethrin comprised between 11-75% of the TRR (total radioactive residues) for field grown crops. The *in vitro* photolysis portion of the study was primarily conducted to aid in the identification of possible photodegradates detected. Allethrin was not detected after 24 hours when exposed to direct sunlight. For the 2-, 5- and 7-day samples the primary residues extracted were a combination of photoproducts, illustrating that allethrin is rapidly degraded in sunlight.

The stored food scenario of the metabolism study is applicable to the proposed use and was performed to simulate the environment of a food handling establishment and study the fate in/on foods in these environments. Allethrin was the principal residue extracted from stored food samples, accounting for approximately 84-94% of the TRR. Trace amounts of various photoproducts were detected in the analyses. A metabolite that consisted of 13.8% of the TRR in lettuce was not identified. The results of the stored food portion of the study show that the parent compound is not significantly degraded producing only trace amounts of epoxides and no allethrolone. Allethrolone, which was found in field grown crops, was the only product identified for which cleaving had occurred; all other photoproducts retained the ester linkage. Based on the submitted study, the residue of concern is the parent compound, allethrin, for tolerance expression and risk assessment purposes.

No livestock metabolism data were submitted with the food handling establishment petition. A nature of the residue study for livestock is required due to the inclusion of granaries, feed processing plants and unoccupied animal quarters as possible application sites on the current VBC Esbiol® 90 Insecticide labels for Esbiothrin and Esbiol. The need for a meat, milk, poultry and eggs magnitude of the residue study will be determined when the required livestock nature of the residue study has been received and reviewed. Alternatively, HED recommends that the petitioner remove any application sites that could result in Esbiol or Esbiothrin residues in/on livestock feed items.

The Environmental Fate and Effects Division concluded that the use of allethrins at food handling establishments (FHEs) would not adversely impact ground or surface water; therefore, a drinking water assessment was not performed and residues of concern for water were not determined (2/28/06 memo, Cheryl Sutton, D323355).

5.2 Dietary Exposure and Risk

Acute and chronic dietary exposure assessments for the allethrins were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 2.03), which incorporates consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. The 1994-96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive

survey days. Foods "as consumed" (e.g., apple pie) are linked to EPA-defined food commodities (e.g. apples, peeled fruit - cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by USDA/ARS and EPA. For chronic exposure assessment, consumption data are averaged for the entire U.S. population and within population subgroups, but for acute exposure assessment are retained as individual consumption events. Based on analysis of the 1994-96, 98 CSFII consumption data, which took into account dietary patterns and survey respondents, HED concluded that it is most appropriate to report risk for the following population subgroups: the general U.S. population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, adults 20-49, females 13-49, and adults 50+ years old.

HED policy does not require an acute dietary exposure analysis for food handling uses. However, the application of allethrins as a space spray produced residues as high as 0.93 ppm for covered food commodities at the lower application rate. For this reason, an acute dietary assessment was conducted.

For acute exposure assessments, individual one-day food consumption data are used on an individual-by-individual basis. The reported consumption amounts of each food item can be multiplied by a residue point estimate and summed to obtain a total daily pesticide exposure for a deterministic exposure assessment, or "matched" in multiple random pairings with residue values and then summed in a probabilistic assessment. The resulting distribution of exposures is expressed as a percentage of the aPAD on both a user (i.e., only those who reported eating relevant commodities/food forms) and a per-capita (i.e., those who reported eating the relevant commodities as well as those who did not) basis. In accordance with HED policy, per capita exposure and risk are reported for all tiers of analysis. However, for tiers 1 and 2, any significant differences in user vs. per capita exposure and risk are specifically identified and noted in the risk assessment.

For chronic dietary exposure assessment, an estimate of the residue level in each food or food-form (e.g., orange or orange juice) on the food commodity residue list is multiplied by the average daily consumption estimate for that food/food form to produce a residue intake estimate. The resulting residue intake estimate for each food/food form is summed with the residue intake estimates for all other food/food forms on the commodity residue list to arrive at the total average estimated exposure. Exposure is expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is performed for each population subgroup.

5.2.1 Acute Dietary Exposure/Risk

An acute dietary exposure assessment was conducted for allethrins. The acute analysis assumed that 100% of food handling establishments and all foods are treated with allethrins. Default DEEM 7.81 processing factors were applied. The highest residue values from each commodity represented in the FHE magnitude of residue study were translated to other food forms within DEEM-FCID™ when appropriate. For foods forms that could not be translated, the highest residue value of 0.93 ppm was used.

HED is concerned when dietary risk exceeds 100% of the PAD. The acute dietary exposure analyses were below the Agency's level of concern. For the U.S. population the exposure was 0.014 mg/kg/day, which utilized 46% of the aPAD. The highest exposure and risk estimates were for children 1-2 years old. At the 95th percentile, the exposure for children 1-2 was 0.027 mg/kg/day, which utilized 90% of the aPAD (see Table 5.2.2).

5.2.2 Chronic Dietary Exposure/Risk

A partially refined chronic dietary exposure assessment was also performed. The assessment included average residue values from the submitted magnitude of residue study, and assumed all foods and 20% of all FHE facilities are treated with allethrins as estimated by BEAD. Default DEEM 7.81 processing factors were applied. Average residue values for each commodity analyzed were translated to other food forms within DEEM-FCID™ when appropriate. For foods forms that could not be translated, the highest average residue value of 0.88 ppm was used.

HED is concerned when dietary risk exceeds 100% of the PAD. The dietary exposure analysis results in chronic dietary risk estimates that are below the Agency's level of concern. For the U.S. population the exposure was 0.0010 mg/kg/day, which utilized 13% of the cPAD. The highest exposure and risk estimates were for children 1-2 years old. The exposure for food only was 0.0024 mg/kg/day, which utilized 31% of the cPAD (see Table 5.2.2).

Esbiothrin is classified as having "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential". Therefore, a cancer dietary assessment was not performed.

Table 5.2.2. Dietary Exposure and Risk for Allethrins						
Population Subgroup	Acute Dietary 95th Percentile			Refined Chronic Dietary		
	aPAD (mg/kg/day)	Dietary Exposure (mg/kg/day)	% aPAD	cPAD (mg/kg/day)	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.03	0.0139	46	0.008	0.00101	13
All Infants (< 1 year old)		0.0206	69		0.00134	17
Children 1-2 years old		**0.0270**	**90**		**0.00244**	**31**
Children 3-5 years old		0.0233	78		0.00212	26
Children 6-12 years old		0.0165	55		0.00142	18
Youth 13-19 years old		0.0115	38		0.000925	12
Adults 20-49 years old		0.00984	33		0.000832	10
Adults 50+ years old		0.00881	29		0.000775	9.7
Females 13-49 years old		0.00937	31		0.000793	9.9

5.3 Anticipated Residues

Anticipated residues based on the submitted MOR study were used for the acute and chronic assessments. In the study, food commodities were exposed to Esbiol with and without commercial packaging, covered and uncovered for 2 hours and 6 hours at two different application rates. The FHE labels for Esbiol and Esbiothrin specify that foods should be covered and treated at the lower application rate. However, the labels do not specify how long foods will be exposed to the pesticide or if foods will be in their commercial packaging during application. Therefore, the ARs presented in Table 5.3 are based on residue levels resulting from covered foods, outside of their commercial packaging at the lower application rate. The acute assessment included the highest residue value from the 2 hour or 6 hour exposure time for each commodity analyzed in the MOR study. The chronic assessment included the average residue value from the 2 hour and 6 hour exposure times for each commodity. The values below were then translated to other food forms within DEEM-FCID™ when appropriate. For food forms that could not be translated, the highest residue value of 0.93 ppm was used for the acute assessment and the highest average residue value of 0.88 ppm was used for the chronic assessment. See "Allethrins: Petition for the Establishment of a Tolerance for Esbiol and Esbiothrin for Use in Food/Feed Handling Establishments. Summary of Analytical Chemistry and Residue Data, DP Barcode 324039" by Toiya Goodlow for additional information.

Commodity	Acute AR	Chronic AR[1]	Origin of Residue
Milk	0.028	0.027	Dairy products, all other milks [coconut, soybean]
Butter	0.26	0.255	Crops groups 14 & 20: tree nuts and oilseeds; milk fat; peanuts; pine nut; all other oils [citrus, coconut, corn field, cottonseed, olive, palm, peppermint, sesame, soybean, spearmint]
Cooked meat	None	0.15[2]	Not used for acute assessment, the higher uncooked meat value used instead
Uncooked meat	0.19	0.15[2]	All meats; poultry; eggs
Flour	0.44	0.32	All flours [arrowroot, barley, buckwheat, chickpea, cornfield, oat, potato, rice, rye, soybean, triticale, wheat]; all grain byproducts [barley bran, corn field meal & bran, oat bran, rice bran, wheat bran & germ]
Rice	0.23	0.19	Rice[white, brown & wild]; all whole grains [amaranth, barley pearled, buckwheat, corn (pop & sweet), millet, oat groats, quinoa, rye, sorghum, wheat]
Bread	None	None	Not used
Lettuce	0.93	0.88	Crop groups 2,4, 5 & 19: leaves of root & tuber, leafy and Brassica leafy vegetables, herbs and spices; ginger; teas; asparagus; belguim endive; peppermint; spearmint
Cooked Apples	0.061	0.0688[3]	All juices [apple, apricot, blackberry, carrot, celery, cherry, cranberry, grape, grapefruit, lemon, lime, mango, orange, papaya, passion fruit, peach, pear, pineapple, prune, raspberry, strawberry, tangerine, tomato, watermelon]
Raw apples	0.096	0.0688[3]	Crop groups 1A,8,9,10,11,12,13: root, fruiting, and cucurbit vegetables, squash/cucumbers, citrus, pome, and stone fruits, all berries; all other fruits [acerola, banana, breadfruit, cherimoya, coconut, cranberry, date, feijoa, fig, canistel, grape, guava, joboticaba, jackfruit, kiwifruit, longan, lychee, mamey apple, mango, mulberry, papaya, passion fruit, pawpaw, persimmon, pineapple, plantain, pomegranate, sapote, Spanish lime, soursop, starfruit, sugar apple, tamarind, tomato tree]
Candy	None	None	Not used
Sugar	0.48	0.295	Beet sugar; corn field syrup & starch; honey; maple sugar & syrup; sugarcane molasses & sugar; sorghum syrup
Default value-highest residue: lettuce	0.93	0.88	Crop groups 3 & 6: bulb and legume vegetables; All other commodities that did not translate [alfalfa seed, artichoke, avocado, bamboo shoots, cactus, carob, cassava, cocoa bean chocolate & powder, coffee, dasheen corm, fish, hop, mushroom, olive, palm heart, potato, psyllium seed, seaweed, sesame seed, sweet potato, tanier corm, tumeric, vinegar, water chestnut, watercress, yam

[1] Chronic AR does not include 20% facilities treated factor. Factor added under Adjustment Factor 2 in DEEM-FCID ™.
[2] Meat average used for the chronic AR is the average of cooked and uncooked meat residues.
[3] Apple average used for the chronic AR is the average of cooked and uncooked apples.

The Biological Economics and Analysis Division provided HED with a projected estimate of the percentage of FHE facilities that may use allethrins to treat pests. BEAD determined that 20% of all food handling establishments may be treated with allethrins based on the available data from registered pesticides currently used in food handling establishments. This value was incorporated into the chronic assessment only; no percent treated value was used in the acute analysis.

5.4 Dietary Risk Characterization

In the course of conducting a refined dietary exposure analysis, decisions are made regarding the following: the residue data used in the analysis (e.g. monitoring data, field trial data, etc.), refinements incorporated in DEEM-FCID™ such as percent crop treated and processing factors, sensitivity analyses, and a variety of other issues which may be chemical- or crop-specific. Characterization of the allethrin dietary assessment and associated uncertainties include:

- Anticipated residues based on the MOR study for food handling establishments were used in the acute and chronic assessment. The residue study was performed using space spray applications, which is the most rigorous type of application (space > general > spot >crack and crevice) for food handling establishment treatments. According to OPPTS Guideline 860.1460 the space spray study can be submitted as a conservative/worst case scenario for all four treatment types, since it is likely to produce the highest residue levels. Therefore, using the highest residue values for the acute analysis and average residue values for the chronic analysis from the space spray study is conservative and may result in an overestimate of dietary risks for less rigorous applications of allethrins.

- Both the acute and chronic assessments assumed that all foods were treated with allethrins (i.e. all commodities listed in DEEM-FCID™ were included in these analyses). This is an extremely conservative assumption that is necessary since it is not possible to determine which foods will be present at the time of application in each food handling establishment.

- BEAD provided HED with a projected estimate of the percentage of FHE facilities that may use allethrins to treat pests. BEAD determined that 20% of all food handling establishments may be treated with allethrins based on the available data from registered pesticides currently used in food handling establishments. This value was incorporated into the chronic assessment only. The acute assessment assumed that 100% of food handling establishments will be treated with allethrins.

6.0 RESIDENTIAL EXPOSURE/RISK CHARACTERIZATION

6.1 Residential Handler Exposure

The term "handler" applies to individuals who mix, load, and apply the pesticide product. Only inhalation exposures have been assessed for the residential handler scenarios. Dermal exposures were not assessed because no dose or endpoints were selected for dermal exposure. Residential handler exposures were assessed for aerosol can application to a variety of use sites. Some allethrin products are packaged as ready to use trigger sprayer bottles. The handler risks calculated from aerosol can application are protective of risks from trigger sprayer applications because the unit exposure values are lower for trigger sprayer application. PHED unit exposure data were used to assess exposures because chemical-specific monitoring data were not available.

The following assumptions were used in estimating risks from residential handler exposure to allethrins:

- The body weight of an adult handler is 70 kg.
- One aerosol can is used per day. This assumption is based upon the HED Science HED Science Advisory Committee on Exposure SOP 12: "Recommended Revisions to the Standard Operating Procedures for Residential Exposure Assessment" (2/22/2001).
- Each aerosol can contains 15 to 16 ounces by weight of product based upon the labels included in the Use Closure Memo.
- The percent ai in the products ranges from 0.10 to 0.25 percent by weight based upon the limitations to be included in the RED.

All of the handler MOEs exceed the target MOE of 1000, therefore, the handler risks are not of concern.

Table 6.1 Residential Handler Risks for Allethrin

Use Scenario	Percent ai in Product	Amount of Product Used per Day	Amount of ai used per day	Inhalation MOE*
Handler Exposures – Aerosol Can Application				
Indoor Surface or Space Spray	0.25	One 15 ounce can	0.0047 lb	29,000
Hand Held Yard and Patio Fogger	0.15	One 16 ounce can	0.0015 lb	46,000
Wasp and Hornet Nests	0.10	One 16 ounce can	0.0010 lb	70,000
*All of the MOEs exceed the target MOE of 1000 and therefore the risks are not of concern.				

6.2. Residential Post Application Exposure

The term "post-application" describes individuals who are exposed to pesticides after entering areas previously treated with pesticides. Allethrin post application incidental oral exposures may occur after surface applications of allethrin are made to residential areas such as carpets and vinyl flooring. Inhalation exposures may occur after space spray application. Incidental oral exposures were assessed for toddlers and inhalation exposures were assessed for adults and toddlers. Dermal exposures were not assessed because no systemic effects were observed at the

limit dose in the dermal toxicity studies in test animals and no toxicity endpoint was selected for dermal exposure. The following scenarios were assessed:

1) Toddler incidental oral ingestion of residues on indoor surfaces after fogger treatment.
2) Toddler incidental oral ingestion of residues on indoor surfaces after PCO broadcast surface treatment.
3) Toddler incidental oral ingestion of residues on indoor surfaces after Consumer spot surface treatment.
4) Inhalation exposures from space spray application
5) Inhalation exposures from mosquito coils and fly mats
6) Inhalation exposures from yard and patio foggers

In the previous version of the ORE assessment (D334788), incidental oral exposures from PCO broadcast surface sprays were assessed at spray dilutions that ranged from 0.25 to 3.0 percent with a spray volume of 1 gallon per 1000 ft^2 and risks of concern were identified. In response to these concerns, the registrants have agreed to limit the spray dilution to 0.05 percent when the spray volume is 1 gallon per 1000 ft^2 or 0.10 percent when the spray volume is 0.50 gallons per 1000 ft^2.

Because many of the consumer applied products contain greater than 0.05 percent allethrins, the residential applications of consumer products will be limited to spot treatments in accordance with the allethrin RED and broadcast surface applications to areas such as rugs and carpets will be eliminated. Some of the existing labels already require spot treatments, for example, the Real Kill label#9688-86 states: "FOR SPOT TREATMENT ONLY - Direct spray into cracks and crevices in walls, dark corners of rooms, cabinets, closets, along and behind baseboards, beneath and behind sinks, stoves, refrigerators and cabinets, around plumbing and other utility installations and wherever else these pests may find entrance". Given that the typical consumer product is an aerosol can which contains approximately 16 ounces by weight, which is roughly equivalent to 16 ounces by volume, and given that spray volume is 1 gallon per 1000 ft^2 as stated in the Allethrin Smart Meeting, the area that could be treated with one can is 125 ft^2 or approximately 10 percent of a typical 1250 ft^2 house.

6.2.1 Residential Post Application Exposure Data

Exposure data for assessing post-application exposures from the use of foggers and aerosols in indoor residential settings were based upon pyrethrin studies conducted by the Non-Dietary Exposure Task Force (NDETF). The pyrethrin study data are considered applicable for allethrin because of the structural similarity between pyrethrin and allethrin.

6.2.2 Residential Post Application Exposure Assumptions

The following assumptions were used in estimating risks from residential post application exposure to allethrins:

General Assumptions

- The body weight of an adult is 70 kg
- The body weight of a toddler is 15 kg
- The breathing rates are 1.0 m^3/hr for adults and 0.7 m^3/hr for children. These values are from SOP #12 and are recommended for scenarios of a few hours in duration.
- Exposure is assessed on day of application (i.e., day zero)
- The application rates were generally taken from the product labels, the Allethrin Smart Meeting or the limits to be established in the RED.

Indoor Fogger Surface Treatment Post Application Exposure Assumptions

- The application rate is 3.6 mg/m^3 based upon the Speer 4X Indoor Fogger (formerly 11715-96, transferred to 2724-552) which is a 1.5 ounce fogger containing 1.2 percent allethrin. It is assumed that one fogger will treat a 5000 ft^3 (141.5 m^3) room as stated on the label.
- The indoor surface residue is 0.65 µg/cm^2 based on NDETF study data for pyrethrin and the above application rate.
- The hand transfer efficiency is 8% for carpet and 11% for vinyl based on NDETF data
- The saliva extraction factor is 50 percent.
- The surface portion of hand put in mouth is 20 cm^2
- The hand-to-mouth (HMT) exposure frequency is 20 times per hour for short term exposures as listed in SOP #12. This is a 90th percentile value from a video observation study of 30 preschool children.
- The HTM exposure frequency is 9.5 times per hour for intermediate term exposures as listed in SOP 12. This is the mean value from the video observation study.
- The exposure duration is 4 hours for hard surface floors and 8 hours for carpeted floors.

PCO Broadcast Indoor Surface Treatment Post Application Exposure Assumptions

- The spray dilution is 0.05 percent when the spray volume is 1 gallon per 1000 square feet.
- The spray dilution is 0.10 percent when the spray volume is 0.5 gallon per 1000 square feet.
- The hand transfer efficiency is 8% for carpet and 11% for vinyl based on NDETF data
- The saliva extraction factor is 50 percent.
- The surface portion of hand put in mouth is 20 cm^2
- The HTM exposure frequency is 20 times per hour for short term exposures.
- The HTM exposure frequency is 9.5 times per hour for intermediate term exposures.
- The exposure duration is 4 hours for hard surface floors and 8 hours for carpeted floors.

Consumer Spot Indoor Surface Treatment Post Application Exposure Assumptions

- The spray dilution ranges from 0.05 to 0.25 percent based upon the consumer product labels and RED limitations.
- One 16 ounce aerosol can is applied based upon the residential SOPs.
- The application will made as a spot treatment as required by the Allethrin RED.
- The spray volume is 1 gallon/1000 ft^2 based on the Allethrin Smart Meeting.
- One can treats 125 ft^2 which is 10 percent of the area of a typical 1250 ft^2 house.
- The exposure duration is 0.4 hours for hard surface floors and 0.8 hours for carpeted floors based upon the Residential SOP values of 4 hours for hard surface floor and 8 hours for

carpeted floors for broadcast application times a correction factor of 0.1 to account for the smaller area treated during spot treatments.
- The hand transfer efficiency is 8% for carpet and 11% for vinyl based on NDETF data
- The saliva extraction factor is 50 percent.
- The surface portion of hand put in mouth is 20 cm^2
- The HTM exposure frequency is 20 times per hour for short term exposures.
- The HTM exposure frequency is 9.5 times per hour for intermediate term exposures.

Space Spray Application Exposure Assumptions
- The products contain 0.1 or 0.2 percent based upon existing labels and the Allethrin RED.
- Two application rates were considered with the lowest rate based upon the amount of spray applied during the NDETF study and the highest rate based upon the Raid label.
- The air concentration of 0.022 mg/m^3 from the NDETF study was adjusted to reflect the above rates.
- The exposure duration is 2 hours because air monitoring, which was conducted for two hours after application, indicated that the air concentrations dropped from an initial value of 0.12 mg/m^3 to 0.014 mg/m^3.

Mosquito Coil and Fly Mat Exposure Assumptions
- The percent a.i. is 0.3 percent for mosquito coils and 24 percent for fly mats based upon the product labels.
- The weight of the mosquito coils and mats is 12 grams and 0.93 grams, respectively, based upon the allethrin smart meetings.
- The duration of emission is 6 hours for a coil and 10 hours for a mat based upon the allethrin smart meetings.
- The number of mats or coils used is two per treatment based upon the residential SOPs.
- The space treated is 90.62 m^3 based upon the a 20 foot by 20 foot patio with a "ceiling height" of 8 feet as specified in the residential SOPs. (3200 ft^3 = 90.62 m^3)
- The initial concentration is calculated as an instant release where all of the material is thrown up into the space as stated in the residential SOPs.
- The time weighted average (TWA) concentration is 100 times less than the initial concentration based upon the residential SOPs.
- The exposure duration is 5 hours for adults and 3 hours for children based upon the Residential SOPs.

Hand Held Yard and Patio Fogger Assumptions
- The percent a.i. is 0.15 based upon the product labels.
- The spray discharge rate is 6 grams of product per second based upon the Allethrin Smart Meeting.
- The spray duration is 3 seconds based upon the Allethrin Smart Meeting.
- The space treated is 90.62 m^3.
- The initial concentration is calculated as an instant release.
- The TWA concentration is 100 times less than the initial concentration.
- The exposure duration is 5 hours for adults and 3 hours for children.

Total Release Yard and Patio Fogger Assumptions

- The percent a.i. is 0.15 based upon the product labels.
- The container size is 1.5 ounces based upon the Raid Yard Guard label 4822-394. The 6.0 ounce size will be eliminated from this label in accordance with the RED.
- The space treated is 90.62 m^3.
- Two containers are used as specified in the Residential SOPs.
- The initial concentration is calculated as an instant release.
- The TWA concentration is 100 times less than the initial concentration.
- The exposure duration is 5 hours for adults and 3 hours for children.

6.2.3 Residential Post Application Risk Estimates

The exposure and risk estimates for the residential post application scenarios are summarized in Table 6.2 and the calculations are included in Appendix A of the Allethrin ORE Assessment. Most of the scenarios are not of concern because the MOEs approach or exceed the target MOE of 1000. The outdoor fogger scenario is of concern for inhalation exposures because the inhalation MOE of 650 does not exceed the target MOE of 1000.

6.3 RESIDENTIAL RISK CHARACTERIZATION

Handler Risks

All of the handler MOEs exceed the target MOE of 1000, therefore, the handler risks are not of concern. The handler risks are conservative because it was assumed that one entire can would be used per day.

Post Application Risks

The yard and patio fogger scenario is only of concern when the product is in the form of a total release fogger. The yard and patio scenario is not of concern when the product is in the form of a hand held fogger. Although both product forms are on the same label (4822-394) the hand held form is more typically found on retail shelves and likely represents the majority of usage. This is supported by the Residential Exposure Joint Venture (REJV) survey which indicated that most of the Allethrin containing Yard and Patio Fogger products in the house hold inventory were hand held foggers. The hand held fogger contains approximately 454 grams of product which is enough for approximately 9 sprays based upon the nozzle discharge rate of 6 grams per second and a spray duration of 9 seconds By contrast, the total release foggers can only be used once because they discharge their entire contents upon activation. It should also be noted that the POD, which is a NOAEL of 1.3 mg/kg/day observed in the inhalation study, may be an artifact of dose spacing because it is five times lower than the LOAEL of 6.5 mg/kg/day. Given that the MOE is 650 with a NOAEL of 1.3 mg/kg/day, only a slightly higher NOAEL of 2.0 mg/kg/day would yield an MOE of 1000. Considering this, HED has minimal concern with an MOE of 650 for this scenario.

Table 6.2 – Allethrin Residential Post Application Risk Summary			
Source of Exposure	**Application Rate**	**Exposed Population**	**MOE***
Incidental Oral Exposures (Short Term)			
Fogger Treatment - Carpet Floors Fogger Treatment - Vinyl Floors	3.6 mg/m^3	Children	3600 5200
PCO Surface Treatment - Carpet Floors PCO Surface Treatment - Vinyl Floors	0.0042 lb ai/1000 ft^2	Children	1200 1700
Consumer Spot Treatment - Carpet Floors Consumer Spot Treatment - Vinyl Floors	0.25% Spray	Children	2200 3400
Consumer Spot Treatment - Carpet Floors Consumer Spot Treatment - Vinyl Floors	0.05% Spray	Children	11000 17000
Incidental Oral Exposures (Intermediate Term)			
Fogger Treatment - Carpet Floors Fogger Treatment - Vinyl Floors	3.6 mg/m^3	Children	3000 4400
PCO Surface Treatment - Carpet Floors PCO Surface Treatment - Vinyl Floors	0.0042 lb ai/1000 ft^2	Children	960 1400
Consumer Spot Treatment - Carpet Floors Consumer Spot Treatment - Vinyl Floors	0.25% Spray	Children	1900 2800
Consumer Spot Treatment - Carpet Floors Consumer Spot Treatment - Vinyl Floors	0.05% Spray	Children	9600 14000
Inhalation Exposures (Short/Intermediate Term)			
Space Spray – 0.25 Percent Product	0.40 mg/m^3 (based upon the NDETF study)	Children Adults	1300 4200
Space Spray – 0.10 Percent Product	0.16 mg/m^3 (based upon the NDETF study)	Children Adults	3050 10000
	0.35 mg/m^3 (Based upon Raid label 4822-513)	Children Adults	1400 4800
Mosquito Coils	2 coils per patio	Children Adults	7000 14000
Fly Mats	2 mats per patio	Children Adults	1800 3600
Hand Held Yard and Patio Fogger	3 second spray per patio (based on the Smart Meeting)	Children Adults	3100 6200
Hand Held Yard and Patio Fogger	9 second spray per patio (Back calculated)	Children Adults	1000 2200
Total Release Yard and Patio Fogger	Two 1.5 ounce foggers per patio	Children Adults	**650** 1300

***MOEs in bold font do not approach or exceed the target MOE of 1000 and indicate risks of concern.**

7.0 AGGREGATE RISK ASSESSMENTS

Aggregate assessments were conducted for incidental oral exposure scenarios because the same study is used for the dietary and incidental oral exposure endpoints based on liver toxicity in dog studies. Inhalation exposure could not be included in the aggregate assessment because the endpoint for inhalation exposure was based on neurotoxicity. Aggregate risk was calculated for combined food and residential exposure for children 1-2 years old. This population was assessed because this age group had the highest dietary exposure and could be expected to receive incidental oral exposure. No endpoints were identified for dermal exposure and the allethrins are not expected to adversely impact ground water, so exposure by these routes was not assessed. As shown below, the short term aggregate MOEs are not of concern for any of the scenarios because they exceed the LOC. An intermediate term aggregate MOE of 750 was estimated for one scenario (PCO Broadcast – Carpet). There is minimal concern for this estimated risk, however, since the intermediate term (continuous exposure over a one to six month period) exposures of toddlers to day zero carpet surface residues is highly unlikely due to dissipation. The MOE of 750 is expected to be protective for this exposure scenario.

Table 7.0. Allethrin Aggregate Risk for Children 1-2 Years Old.

Exposure Scenario	POD mg/kg/day	LOC[1]	Food Exposure[2] mg/kg/day	Residential Exposure[3] mg/kg/day	Aggregate Exposure[4] mg/kg/day	Aggregate MOE[5]
Short-term Exposure						
Fogger – carpet	20 (NOAEL)	1000	0.0024	0.0056	0.0080	2500
Fogger – vinyl floor				0.0039	0.0063	3200
PCO Broadcast – carpet				0.017	0.019	1100
PCO Broadcast – vinyl				0.012	0.014	1400
Consumer Spot Treatment - carpet				0.0090	0.011	1800
Consumer Spot Treatment - carpet				0.0060	0.0084	2400
Intermediate-term Exposure						
Fogger – carpet	8 ($BMDL_{10}$)	1000	0.0024	0.0027	0.0051	1600
Fogger – vinyl floor				0.0018	0.0042	1900
PCO Broadcast – carpet				0.0083	0.0107	**750**
PCO Broadcast - vinyl				0.0057	0.0081	990
Consumer Spot Treatment - carpet				0.0042	0.0066	1200
Consumer Spot Treatment - carpet				0.0029	0.0053	1500

[1]Level of Concern (LOC) based on 10x uncertainty factor for interspecies extrapolation, 10x for intraspecies variability, and 10x for lack of a developmental neurotoxicity study.
[2] Refined chronic dietary exposure for children 1-2 years old (Table 5.2.2)
[3] Residential Exposure = Incidental oral exposure from the Allethrin ORE Assessment.
[4]Aggregate Exposure = Food Exposure + Residential Exposure
[5]Aggregate MOE = POD / Aggregate Exposure

8.0 CUMULATIVE RISK ASSESSMENT

Section 408 of the FFDCA states that the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." EPA has not made a common mechanism of toxicity finding as to the allethrins and any other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that allethrins have a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 OCCUPATIONAL EXPOSURES AND RISK

9.1 Occupational Handler Risk

The term "handler" applies to individuals who mix, load, and apply the pesticide product. Because most allethrin products are packaged in aerosol cans, most of the allethrin uses involve only application. There are a few products packaged as ready to use liquids or liquid concentrates, which are applied with mechanical sprayers, compressed air sprayers or foggers. These products are used in commercial/ industrial/institutional areas, non-food greenhouses and non-food animal premises.

PHED Exposure Data

It is the policy of the HED to use data from the Pesticide Handlers Exposure Database (PHED) when chemical-specific monitoring data or other handler-specific data are not available. PHED was designed by a task force of representatives from the US. EPA, Health Canada, the California Department of Pesticide Regulation, and members of the American Crop Protection Association. The PHED exposure data were used for the low pressure handwand/back sprayer, aerosol can and HP handwand scenarios. The low pressure handwand and back sprayer scenarios were combined because they have the same inhalation unit exposures.

Fogger Exposure Data

In the previous assessment, data from two studies were used to estimate worker exposures during fogging applications. These studies include a University of Florida study on greenhouse applicators (Nigg et. al., 1987) and an MGK study that monitored applicator exposure to prallethrin during ULV cold fogging (Bergman, 2002). Both the Nigg study and MGK study have data quality concerns because only one worker was monitored. The MGK study also has ethics concerns because proper informed consent procedures were not followed. Based upon these concerns, the OPP Ethics Reviewer and HED Management decided that neither study should be used for risk assessment. (EPA, 2007). These studies have thus been deleted from this assessment.

The following assumptions were used in estimating risks to occupational handlers from exposure to allethrins:

- The body weight of an adult handler is 70 kg.
- The exposure duration ranges from short to long term. (Note – The endpoint for inhalation exposures is the same for all durations of exposure)
- Respiratory protection either not worn (No Resp.) or consists of a filtering facepiece dustmask (PF5 Resp.) or a full face piece respirator (PF50).
- The application rates for low pressure handwand/backpack sprayer and high pressure handwand are from the PCO product labels and are expressed in terms of product dilution rather than area treated.
- The application rate for PCO aerosol can application is from label 5602-192.
- Undiluted products could be used for space sprays, contact sprays, surface sprays and crack and crevice treatments at a wide variety of commercial, industrial and institution sites as listed on the labels.
- Dilute sprays could be used for foliar applications in greenhouses.
- A greenhouse applicator could apply 1000 gallons of a dilute spray solution per day using a high-pressure hand-wand based upon ExpoSAC Policy #9.
- For standard surface spray applications, a PCO could apply 40 gallons of undiluted pesticide solution per day using a low pressure hand-wand or backpack sprayer. This assumption is from ExpoSAC Policy #9.
- The application rate concentration for space sprays (i.e. fogging) is based upon the application of 1.0 ounce of spray per 1000 cubic feet based upon product labels.
- The space spray fogging applicator would be exposed to the average of the initial concentration and the application rate concentration during hand held fogging.
- The fogging applicator will be exposed to average concentration for 240 minutes per 480 minute work day with the unexposed time being spent in transportation and setup. If an Actisol Commercial Unit is used as is specified on the labels, the applicator could treat 134,000 cubic feet in 240 minutes. This is based upon the spray output of the Actisol unit (0.56 ounces per minute @ 15 PSI).

Occupational Handler Risk Summary:

Only inhalation exposures have been assessed. Dermal exposures were not assessed because no dose or endpoints were selected for dermal exposure. The target MOE is 100 for short, intermediate and long term inhalation exposures. Risk estimates for the surface spray scenarios are summarized in Table 9.1 and the risk estimated for the space spray scenario is summarized in Table 9.2. The calculations are detailed in Appendix A of the ORE Assessment.

Most of the surface spray inhalation MOEs are above the target MOE of 100 without respirators (i.e. No Resp.) and therefore the inhalation risks are not of concern. The high pressure handwand scenario is of concern without respirators and requires a PF5 filtering facepiece respirator (i.e. a dust mask) to achieve the target MOE.

Table 9.1 – Occupational Handler Risks from Surface Spray Applications					
Exposure Scenario	**Dilution**	**Spray Dilution (Percent ai)**	**Amount Sprayed per Day**	**lb ai handled per day**	**Inhalation MOE**
M/L/A liquids with LP hand-wand or backpack sprayer	Undiluted	1.5	40 gallons	5	600 – No Resp.
M/L/A liquids with LP hand-wand or backpack sprayer	Diluted in water	0.11	40 gallons	0.37	8100 – No Resp.
M/L/A liquids with HP hand-wand (Greenhouse Use)	Diluted in water	0.11	1000 gallons	9.2	**81 – No Resp.** 400 – PF5 Resp.
Aerosol Can application	Undiluted	0.54	*6 cans* (16 oz ea)	0.032	2300 – No Resp.
MOEs highlighted in bold font indicate risks of concern because they do not exceed the target MOE of 100.					

The MOEs for space spray applications are of concern when respirators are not worn. The MOEs are not of concern if PF50 Full Face Respirators with appropriate cartridges are worn.

Table 9.2 – Occupational Handler Risks from Space Spray Applications					
Label #	**Spray Dilution**	**Application Rate (lb ai/1000 ft^3)**	**Average Concentration (mg/m^3)**	**Respirator Worn**	**Inhalation MOE**
1021-1478	1.5	0.0010	8.0	None	**2.8**
1021-1453	1.0	0.00067	5.4		**4.2**
1021-1478	1.5	0.0010	8.0	PF50 Full	140
1021-1453	1.0	0.00067	5.4	Face	210
MOEs highlighted in bold font indicate risks of concern because they do not exceed the target MOE of 100.					

Occupational Handler Risk Characterization:

It is likely that space spray applications to larger spaces are done using automatic equipment which reduces operator exposure. Additional exposure data and information regarding space spray application methods could be used to refine the risks.

9.2 Occupational Post Application Risk

Allethrins are used as space sprays in a wide variety of indoor areas such as barns, greenhouses, and residences. For many of the applications there are restrictions such as "Do not apply when people are present" or "Do not allow unprotected persons to enter until treated area has been thoroughly ventilated" which minimize post application exposures. There is one product (Misty Mizer Insecticide III, 10807-69) which is applied from a time metered device; however, the label requires that the device be set to operate only 12 hours per day during off hours.

Given the above use characteristics, occupational post application inhalation exposures are anticipated primarily from time metered device applications. To assess these exposures, a scenario that involves the metered release into an industrial work area was evaluated based upon the Misty Mizer label #10807-69. No exposure data was available to assess post application exposures.

The inhalation MOE is 850, which exceeds the target MOE of 100 and is not of concern. This MOE is representative of a space that is ventilated at the rate of 0.20 air changes per hour at night and 1.0 air changes per hour during the day.

The risk for the metered release scenario is conservative because it was assumed that the aerosols would remain airborne until they were removed by ventilation and the effects of aerosol settling were not considered. Aerosol settling could be a major factor depending upon the aerosol size and rate of evaporation. Information regarding the aerosol size and evaporation rate could be used to refine the risks.

10.0 DATA NEEDS AND LABEL REQUIREMENTS

Toxicology

Developmental Neurotoxicity Study

A developmental neurotoxicity (DNT) study is required for the allethrins. However, the Agency is currently evaluating whether a DNT or another comparative toxicity study measuring different endpoints would be best suited for addressing the concern for sensitivity to young animals. The registrants should consult with EPA before beginning this study.

Residue Chemistry

860.1200 Directions for Use

HED recommends the removal of granaries, feed processing plants, unoccupied animal quarters and any other FHEs that store livestock feeds as possible application sites from the current VBC Esbiol® 90 Insecticide labels. Alternatively, the Agency must require the submission of a nature of the residue study for livestock (Guideline 860.1300) and reserve the right to require a meat, milk, poultry and eggs magnitude of the residue study (Guideline 860.1480) if necessary.

Clarification is requested for the use directions for each of the four proposed treatment applications (space and general spray, spot and crack and crevice treatments). Use directions should be explicitly stated for each proposed FHE treatment type.

HED recommends that the VBS Esbiol® and Esbiothrin® 90 Insecticide labels be revised to restrict any FHE applications while food processing is underway for all types of food/feed processing plants.

The submitted labels should also be revised to include food restrictions for the spot and crack and crevice treatment applications (e.g. cover or remove foods before treatment or ventilate treated area). Currently, there are no limitations specified for these two types of FHE applications.

860.1300 Nature of the Residue – Livestock

A nature of the residue study for livestock is required due to the inclusion of granaries, feed processing plants, unoccupied animal quarters and any other FHEs that store livestock feeds as possible application sites on the current VBC Esbiol® 90 Insecticide labels for Esbiothrin and Esbiol. Provided the labels are revised to remove these use sites, a livestock metabolism study will not be required.

860.1480 Meat, Milk, Poultry, and Eggs

The requirement of a meat, milk, poultry and eggs study is reserved until the livestock nature of the residue study has been received and reviewed.

860.1520 Processed Food and Feed

Pilot processing studies are required demonstrating the concentration/reduction of residue levels in/on the raw agricultural commodities potato tubers and wheat. Food handling establishment treatments can potentially be applied at multiple stages of processing. If there is not significant reduction of total allethrin residues in/on food commodities, residue levels may exceed the recommended 1 ppm tolerance for FHE uses. The petitioner is required to submit processing data for potato flakes only for potato tubers, and all wheat processed commodities which includes wheat bran, flour, middlings, shorts and germ. Additional processing studies may be required if residue levels are not reduced by 50% or more in the processed fractions of potato tubers and wheat.

860.1550 Proposed Tolerances

The petitioner is required to submit a revised Section F to specify a tolerance level of 1.0 ppm for total allethrin residues including d-trans chrysanthemic acid of d-allethrolone, d-trans chrysanthemic acid of l-allethrolone, d-cis chrysanthemic acid of d-allethrolone, and d-cis chrysanthemic acid of l-allethrolone in/on all foods in food handling establishments. Since the analytical method submitted is not capable of distinguishing between allethrin isomers and reports total allethrin, the tolerance should also be expressed as total allethrin.

860.1650 Submittal of Analytical Reference Standards

Analytical reference standards for the complete allethrin series of pyrethroids are not currently available in the National Pesticide Standards Repository. Standards for Bioallethrin (004003) and Pynamin Forte (004005) are expired, and no reference standard is available for Esbiothrin (004007). The reference standards should be sent to the Analytical Chemistry Lab, which is located at Fort Meade, to the attention of Theresa Cole or Frederic Siegelman at the following address:

USEPA
National Pesticide Standards Repository/Analytical Chemistry Branch/OPP
701 Mapes Road
Fort George G. Meade, MD 20755-5350

Note: Mail will be returned if the extended zip code is not used.

Occupational and Residential Exposure

875.1400 Inhalation Exposure Indoor

A inhalation exposure study is required for the occupational handler fogger scenario (Mix/Load/Apply liquids with fogger) due to lack of adequate data.

REFERENCES:

Allethrins: Acute and Chronic Dietary Exposure and Risk Assessments for the Section 3 Registration Action for the Use of Esbiothrin and Esbiol in Food Handling Establishments. Toiya Goodlow. DP Barcode 294724.

Allethrins: Petition for the Establishment of a Tolerance for Esbiothrin and Esbiol for Use in Food/Feed Handling Establishments. Summary of Analytical Chemistry and Residue Data. Petition Number: 6H5743. DP Barcode 324039.

Allethrins: Revised Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision (RED). Timothy Dole. DP Barcode D340744.

Esbiothrin: Report of the Cancer Assessment Review Committee. Jessica Kidwell. TXR 0051399. 12/2/03.

EPA, 2007. "Re: Use of the Prallethrin and/or Nigg Studies", Email from John Carley to Molly Clayton, March 1, 2007

Benchmark Dose Analysis of 6-Month Dose Feeding Study of Bioallethrin in Dogs, Philip Villanueva and Kit Farwell. DP Barcode D339909.

Appendix A: Toxicology Assessment

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for food use for the allethrins are listed below. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	-
870.3465	90-Day Inhalation	yes	yes [a]
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes [b]
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5xxx	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	no	-
870.6100b	90-Day Neurotoxicity (hen)	no	-
870.6200a	Acute Neurotox. Screening Battery (rat)	no	yes
870.6200b	90-Day Neuro. Screening Battery (rat)	yes	yes
870.6300	Developmental Neurotoxicity	yes [c]	no
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	no	
Special Studies for Ocular Effects			
	Acute Oral (rat)	no	-
	Subchronic Oral (rat)	no	-
	Six-month Oral (dog)	no	

a Requirement for 90-day inhalation study satisfied by 28-day inhalation study.
b Requirement for chronic toxicity study satisfied by combined chronic/oncogenicity study
c May be satisfied with a comparative neurotoxicity study.

A.2 Toxicity Profiles

Acute Toxicity of Bioallethrin

Guideline	Study Type	MRID	Results	Tox Category
870.1100	Acute Oral	00151444	LD_{50} 709 mg/kg (M) 1042 mg/kg (F)	III
870.1200	Acute Dermal	41155801	LD_{50} > 3000 mg/kg (M&F)	III
870.1300	Acute Inhalation	42906902	LC_{50} : 2.51 mg/L	IV
870.2400	Primary Eye Irritation	41155803	Slight to moderate irritant	III
870.2500	Primary Skin Irritation	41155805	Very slight dermal irritant	IV
870.2600	Dermal Sensitization	41155807	negative	N/A

Acute Toxicity of Esbiol

Guideline	Study Type	MRID	Results	Tox Category
870.1100	Acute Oral	00151460	LD_{50} : 574.5 mg/kg (M) 412.9 mg/kg (F)	II
870.1200	Acute Dermal	41155802	LD_{50} > 2000 mg/kg	III
870.1300	Acute Inhalation	41670801	LC_{50} : 1.32 mg/L (M) 1.23 mg/L (F)	III
870.2400	Primary Eye Irritation	41155804	Moderate ocular irritant	III
870.2500	Primary Skin Irritation	41155806	Not a dermal irritant.	IV
870.2600	Dermal Sensitization	41155808	Not a sensitizer	N/A

Acute Toxicity of Esbiothrin

Guideline	Study Type	MRID	Results	Tox Category
870.1100	Acute Oral	00151449	LD_{50} 432 mg/kg (M) 378.0 mg/kg (F)	II
870.1200	Acute Dermal	00151451	LD_{50} > 2000 mg/kg	III
870.1300	Acute Inhalation	00151452	LC_{50} : 2.63 g/m^3 - unacceptable	III
870.2400	Primary Eye Irritation	00151454	Minimally	IV
870.2500	Primary Skin Irritation	00151453	Slightly	III
870.2600	Dermal Sensitization	42907001	negative	N/A

Acute Toxicity of Pynamin Forte

Guideline	Study Type	MRID	Results	Tox Category
870.1100	Acute Oral	41017101	M: 2150 mg/kg F: 900 mg/kg	III
870.1200	Acute Dermal	41017102	M: 2660 mg/kg F: 4390 mg/kg	III
870.1300	Acute Inhalation	41017103	LC50 > 3.875 mg/L	
870.2400	Primary Eye Irritation	41017104	slight irritant	III
870.2500	Primary Skin Irritation	41017104	negative	IV
870.2600	Dermal Sensitization	41017105	negative	N/A

Summary of Allethrin Toxicity Database				
	Esbiol (S-Bioallethrin) >90% d- trans d-	**Esbiothrin** 72% d- trans d-	**Bioallethrin** 46% d- trans d-	**Pynamin Forte** (d-allethrin) 36% d- trans d-
Acute Neurotoxicity- gavage	NOAEL = 30 mkd LOAEL = 90 mkd: FOB (hunched posture, tremors, abnormal gait, ↓grip strength) 1997. 5, 30, 90 mkd			
Subchronic Neurotoxicity	NOAEL = 144 mg/kg/day LOAEL = 452 mkd: ↓BW, no neurotox observed. Unacceptable (no positive control data) 2000. 75, 250, 2000, 6000 ppm 5, 6.5, 18, 144, 452 mkd			
90-day rat	NOAEL = 18 mkd LOAEL = 37 mkd: micro pituitary changes (M) 149 mkd: ↓BW; ↑liver/ thyroid wt, thyroid micro changes 594 mkd: micro liver changes. 1996. 250, 500, 2000, 8000 ppm 18, 37, 149, 594 mkd		NOAEL = 75 mkd LOAEL = 250 mkd: ↓BW gain; ↑ liver enzymes; ↑abs/rel liver wt 1972. Unacceptable (no supporting tables) 500, 1500, 5000, 10000 ppm 25, 75, 250, 500 mkd	
Chronic/Cancer rat		NOAEL = 27 mkd LOAEL = 83 mkd: ↓BW (F); ↑ liver enzymes, liver micro. renal tubular adenomas: HDT males 1990. 100, 500, 1500,4500 ppm 5.5, 27, 83, 259 mkd		NOAEL = 29 mkd LOAEL = 120 mkd: ↓BW (F), ↑liver wt (M) Negative for tumor response 1985. 125, 500, 2000 ppm 6, 24, 102 mkd

Summary of Allethrin Toxicity Database				
	Esbiol (S-Bioallethrin) >90% d- trans d-	**Esbiothrin** 72% d- trans d-	**Bioallethrin** 46% d- trans d-	**Pynamin Forte** (d-allethrin) 36% d- trans d-
Subchronic mouse		NOAEL = 229 mkd LOAEL = 420 mkd: ↑liver wt and alkaline phosphatase (115%) 1621 mkd, piloerection and hunched posture during weeks 3/4. 1986. 8- week study. 100, 1000, 2000, 4000, 8000 ppm 22, 229, 420, 843, 1621 mkd		NOAEL = 14 mkd LOAEL = 43 mkd - enlarged hepatocytes 1986. 5-week study. 423 mkd: ↑ liver wt 1522 mkd: ↓BW (83%/92%↓PCV (43% vs 48%), ↑SGPT (45 vs 31) 1986. 100, 300, 1000, 3000, 10000 ppm 14, 43, 144, 423, 1550 mkd
Cancer mouse		NOAEL = 214 mkd, HDT No treatment-related tumors. 1990. 50, 250, 1250 ppm 8, 42, 214 mkd		NOAEL = 72 mkd, HDT LOAEL = 350 mkd: ↑rel liver wt. microscopic liver changes. No incr in tumors. 1989 200, 600, 3000 ppm 14, 72, 350 mkd
Developmental rats	Maternal NOAEL = 20 mkd LOAEL = 80 mkd: clinical signs, mortality Devel NOAEL = 80 mkd, HDT LOAEL > 80 mkd 1998. 5, 20, 80 mkd	Maternal NOAEL = 25 mkd LOAEL = 125 mkd: clinical signs, mortality Develop NOAEL = 125 mkd, HDT LOAEL > 125 mkd 1990. 5, 25, 125 mkd	Maternal NOAEL = 125 mkd LOAEL = 195 mkd (mortality) Devel NOAEL = 195 mkd 1979. 50, 125, 195 mkd Note: Not a reliable study for endpoint selection.	Maternal NOAEL = 30 mkd LOAEL = 100 mkd: tremors,↓wt gain Develop NOAEL = 100 mkd HDT 1989. 10, 30, 100 mkd
Developmental rabbit	Maternal NOAEL = 50 mkd LOAEL = 200 mkd: ↓BW gain, tremors Devel NOAEL = 50 mkd, Devel LOAEL = 200 mkd: ↓ossification. 1998. 5, 50, 200 mkd	Maternal NOAEL = 100 mkd LOAEL = 300 mkd: mortality and clinical signs Develop NOAEL = 300 mkd, HDT LOAEL > 300 mkd 1990. 30, 100, 300 mkd.		Maternal NOAEL = 100 mkd LOAEL = 350 mkd: mortality, ↓BW gain Developmental NOAEL = 100 mkd LOAEL = 350 mkd: rib/rib-vertebral malformations 1989. 30, 100, 350 mkd
Reproduction		Parental NOAEL = 50 mkd LOAEL = 150 mkd: ↓body weight Offspring NOAEL = 50 mkd		parental NOAEL = 13 mkd LOAEL = 130 mkd: ↓BW ↑liver wt, and microscopic liver changes

Summary of Allethrin Toxicity Database

	Esbiol (S-Bioallethrin) >90% d- trans d-	**Esbiothrin** 72% d- trans d-	**Bioallethrin** 46% d- trans d-	**Pynamin Forte** (d-allethrin) 36% d- trans d-
		LOAEL = 150 mkd: ↓viability BW gain, marginal increase in delayed developmental milestones (eye opening, auricular duct opening) 1988. 70, 200, 600, 1800 ppm 6, 17, 50, 150 mkd		offspring NOAEL = 13 mkd LOAEL = 145 mkd, ↓pup wt in F2 generation 1989. 200, 2000, 6000 ppm 13, 130, 387 mkd
Subchronic dog feeding	NOAEL = 38 mkd LOAEL – 90 mkd: ↓BW, clinical signs, ↑ liver wt 1996. 90-day feeding study. 400, 1000, 2250 ppm 16, 38, 90 mkd	NOAEL = 20 mkd LOAEL = 63 mkd: ↑liver wt, enzymes. 153 mkd: clinical signs and death 1986. 4-week feeding study. 50, 200, 800, 3200, 6400 ppm 1, 4.5, 20, 63, 153 mkd		
Chronic dog feeding		NOAEL = 70 mkd HDT LOAEL > 70 mkd 70 mkd: alkaline phosphatase ↑ 240% relative to controls, brown/ black livers, ↑ liver/thyroid wt. 1987. 1-year feeding study. 80, 400, 2000 ppm 3, 14, 70 mkd	NOAEL = 6 mkd LOAEL = 36 mkd: microscopic liver changes. 162 mkd: ↑liver enzymes, cardiac arrhythmias, trembling, ↓wt gain 1982. 6- month feeding study. 200, 1000, 5000 ppm 6, 36, 162 mkd	
Chronic dog capsule				NOAEL = 6 mkd LOAEL = 20 mkd: clinical signs 1989. 6, 20, 60, 100 mkd (capsule)
21-day dermal rabbit		systemic NOAEL = 1000 mkd, HDT 1990. 40, 200, 1000 mkd		systemic NOAEL = 300 mkd, HDT 1990 3, 10, 30, 300 mkd
28-day dermal rat	systemic NOAEL = 1000 mkd, highest dose tested dermal NOAEL = 1000 mkd, highest dose tested			

Summary of Allethrin Toxicity Database				
	Esbiol (S-Bioallethrin) >90% d- trans d-	**Esbiothrin** 72% d- trans d-	**Bioallethrin** 46% d- trans d-	**Pynamin Forte** (d-allethrin) 36% d- trans d-
	1998. 10, 100, 1000 mkd			
28-day inhalation - rat	NOAEL = 1.3 mkd LOAEL = 6.5 mkd based on clinical signs in females (limb tremors, hunched posture, vocalization during handling) 1997. 0.0051, 0.025, 0.073 mg/L 1.3, 6.5, 19 mkd			Unacceptable study
Metabolism / PK			Urinary elimination ~ 25-50%; fecal elimination ~ 50-60% in different groups. Several metabolites identified.	
Dermal Absorption	Unacceptable study, not upgradeable			

NOTE: For feeding studies, doses in mg/kg/day are reported for males.
HDT = highest dose tested

Appendix B: Tolerance Reassessment Summary and Table

For the purposes of petition 6H5743, HED has determined that the residue of concern is the parent compound, allethrin. No Codex, Canadian, or Mexican MRLs have been established for the allethrins. Adequate residue data for food handling establishment uses are available.

VBS proposed the establishment of a 1.0 ppm tolerance for Esbiothrin and Esbiol use in food FHE for all foods and feeds. A revised section F must be submitted reflecting the recommended tolerance for total allethrin and the correct commodity definition as specified in appendix Table C.1. Since the analytical method submitted is not capable of distinguishing between allethrin isomers and reports total allethrin, the tolerance should also be expressed as total allethrin.

Provided that the residue chemistry deficiencies outlined in this document are fulfilled, the available data will support a 1.0 ppm tolerance for residues of total allethrin on all foods treated in food handling establishments.

TABLE C.1. Tolerance Summary for Esbiol and Esbiothrin

Commodity	Established/Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments; Correct Commodity Definition
All food items in food handling establishments	1.0	1.0	A tolerance of 1.0 ppm is established for total allethrin residues including **d-trans** chrysanthemic acid of **d**-allethrolone, **d-trans** chrysanthemic acid of **l**-allethrolone, **d-cis** chrysanthemic acid of **d**-allethrolone, and **d-cis** chrysanthemic acid of **l**-allethrolone in or on all food items in food handling establishments.

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R149953

Chemical: d-trans-Chrysanthemum monocarboxylic ester of dl-2-allyl-4-hydroxy-3-methyl-2-cyclopenten-*l*-one

PC Code: 004003
HED File Code: 14000 Risk Reviews
Memo Date: 6/27/2007
File ID: DPD337992
Accession #: 412-07-0208

HED Records Reference Center
7/26/2007